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July 10, 1974

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Research Advances

Inner City Children...

INGESTION OF HOUSE DUST MAY BE SOURCE OF LEAD EXPOSURE

Ingestion of lead-containing household dust by hand-to-mouth activities may be a possible source of lead exposure in inner city preschool children. Dust analyses show that more lead is found on the interior surfaces of inner city houses than in suburban homes.

According to investigators Jaroslav J. Vostal, M.D., Ph.D., Ellen Taves, James W. Sayre, M.D., and Evan Charney, M.D., at the University of Rochester School of Medicine and Dentistry, this hypothesis can offer an explanation for the differences found in blood lead levels among city and suburban children. Their work is supported in part by a grant from the National Institute of General Medical Sciences.

The scientists developed a method to test lead in the dust from inner city household surfaces and on children's hands. Results suggest the route of increased lead intake to be contamination of the hands through contact with the dusty surfaces, followed by ingestion of lead-containing dust when the child puts his hand in his mouth.

In a comparative study of children living in inner city houses and suburban areas, the investigators used disposable paper towels treated with denatured alcohol and a germicide in a "smear and wipe procedure" to collect the dust samples.

In one test, they attempted to determine if significant differences in surface contamination could be found between the older, deteriorating inner

(more)

city homes and the newer suburban ones. In both the inner city and suburban houses, they tested children between the ages of nine months and six years. At least one child in each inner city household previously had a blood level of 40 micrograms of lead per 100 milliliters of blood or more. The investigators collected samples from 44 children living in the old, damaged inner city houses; from 10 children living in old, but repainted inner city dwellings; from 50 children living in the suburbs. They report that the level of hand contamination showed a significant relationship to the household dust level. Greater amounts of lead were found in the inner city samplings than in those from the suburbs.

In another test, they determined the range of lead concentration found in the floor smears from the different types of housing.

These results show that lead-containing dust is present on inner city household surfaces and, consequently, on children's hands. The investigators suggest, then, that dust may be a source of lead exposure. Their data, in fact, confirm that the presence of median lead concentrations on the interiors of inner city houses is approximately five times higher than the interiors of suburban homes.

According to the scientists, the theory implies that lead on the children's hands is ingested and absorbed in quantities sufficient enough to result in an elevated blood level; however, at present, there is no direct evidence to support or confirm this idea.

Increased lead exposure in preschool inner city children is associated with other environmental factors such as peeling paint or inhalation or

(more)

ingestion of street dust, presumably from automotive emissions. However, since exposure is characteristic of children under age five, there is strong support for the hand-to-mouth route identified in this investigation.

The study data do not indicate the source of lead in contaminated households or whether it originates inside or outside the home. But regardless of the origin, the investigators feel that the direct relationship they have found between lead-containing dust in households and the levels on children's hands can offer a new explanation for lead exposure of children living in the inner city.

The investigators published their findings in *Environmental Health Perspectives*, May 1974.

#

This article was prepared by Dorothy Mastin, NIH Summer Information Aide.

TRAUMA--Infection is a major cause of death in traumatized patients who survive the early hazards of shock and respiratory insufficiency, according to the National Institutes of Health.

Research Advances

SCIENTISTS FIND ANIMAL MODEL FOR PERIODONTAL DISEASE

National Institute of Dental Research grantees propose using *Macaca speciosa*, an old world monkey, as an animal model for studies of plaque and periodontal disease. These docile animals are large enough for investigators to use regular dental instruments, they have mouths and teeth which resemble a human's, and their reactions to disease factors are similar to man's.

A good animal model is needed for studies requiring radioactive compounds, strict dietary controls, extensive biopsies, and testing of experimental antibacterial agents. Baboons are too fierce and expensive, marmosets are not sufficiently similar to humans, and some monkeys are too small. Studies undertaken so far to characterize the *Macaca speciosa*, in relation to periodontal disease have been extremely encouraging.

Robert J. Genco, D.D.S., Ph.D., and associates at the State University of New York at Bufallo, scored these young adult monkeys according to gingival, plaque, and calculus indices. Then, they scaled the teeth and for two weeks brushed and flossed them daily to achieve as good oral health as possible. They also X-rayed the monkeys' jaws to determine the condition of their jawbones. Thereafter, all cleaning ceased, and the animals were fed water-softened animal biscuits and bananas for 70 days when they were again X-rayed. Biopsies were taken, plaque was sampled for bacterial analyses, and teeth were re-scored at intervals during the experiment.

The investigators found that the animals reacted in all respects as humans do. Even the changes that occurred with time in bacterial components

(more)

of plaque were similar, although the bacterial strains probably differ. Like human gingivae, the gingival tissue of these monkeys became inflamed when the diet was soft and the teeth were not cleaned. Histologically and ultrastructurally through the electron microscope, the two were indistinguishable. Also, the scientists found that, in culture, normal and inflamed gingival tissues stimulated bone resorption as human tissues do.

In further experiments, the researchers made a quantitative analysis of changes in inflammatory cells during a 10 week period of experimental gingivitis. During the first two weeks, granulocytes were prominent. By four weeks, lymphocytes were most common, and at 10 weeks, plasma cells which make antibodies were the chief tissue infiltrators.

This survey suggests that as gingival inflammation becomes more chronic, local production of antibody in a particular area probably increases. These studies may resolve the question of why investigators have found different types of cells predominant in inflamed gingival tissues.

Some of this research was reported in the August 1973 issue of the *Journal of Periodontology*, and some at the March 1974 meeting of the International Association for Dental Research held in Atlanta, Georgia. Working with Dr. Genco are George Krygier, D.D.S., D.Sc.Od.; Paul A Mashimo, D.D.S., Ph.D.; Ernest Hausmann, D.M.D., Ph.D.; Solon A Ellison, D.D.S., Ph.D.; and Michael Meenaghan, D.D.S., Ph.D.

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Research Advances

ADDICT IS HIS OWN SOURCE OF BACTERIAL ENDOCARDITIS

Bacterial endocarditis is one of the most serious medical complications among the 650,000 heroin addicts in this country. Therapy for this infection of the endocardium is prolonged and the associated morbidity and mortality are high.

The source of bacteria causing endocarditis has not been documented, but many reports have assumed that the most likely sources would be contaminated needles, syringes, or the injected drug itself.

Now, investigators at the Howard University College of Medicine, Washington, D.C., report that these are not the sources of the organism. Rather, the sources of the *Staphylococcus aureus* organism may actually be the addict himself or the diluent for his powdered drug.

The Howard University investigators reached these conclusions after they were unable to isolate *S. aureus* from 100 samples of street heroin or 100 sets of injection paraphernalia. The heroin was obtained by the Bureau of Narcotics and Dangerous Drugs either from undercover purchases off the street or through confiscations during a period covering May through November 1972.

Similarly, the injection paraphernalia was obtained during the same period. Some of the syringes contained blood used by the addicts to rinse the last drop of drug from inside the syringe.

Previous studies have reported *S. aureus* to be the most common infectious agent in bacterial endocarditis of drug addicts, causing 90 percent of the cases of the disease in Washington, D.C.

(more)

Endocarditis (Cont'd)

However, of the 257 organisms cultured from the samples of heroin and injection paraphernalia, the investigators failed to recover a single *S. aureus*, even though they found a wide variety of other microorganisms. Based on this, the investigators state "without reservation" that the heroin and paraphernalia are not the sources of these bacteria. Rather, it is the diluent used to dissolve the powdered drug or the skin and mucous membranes of the addicts themselves that are to blame.

Carmelita U. Tuazon, M.D., Ruth Hill, and John N. Sheagren, M.D., of the Division of Infectious Diseases, reported their findings in *The Journal of Infectious Diseases*, March 1974. Their work was supported by a grant from the National Institute of Allergy and Infectious Diseases.

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PREMATURE BIRTH--Current studies concerning the controls on the duration of gestation and the events leading to the initiation of labor may eventually result in the reduction of the number of infants born prior to term, according to the National Institutes of Health.

News Feature

CONTROL OF BLACK LUNG DISEASE REQUIRES PREVENTIVE MEASURES

Approximately 100,000 Americans are afflicted each year with black lung disease (coal workers' pneumoconiosis), the most lethal of the various dust-inhalation diseases. The key to its control is application of known preventive measures, because the disease is irreversible once established.

The National Heart and Lung Institute's (NHLI) Division of Lung Diseases supports research on black lung disease and the other pneumoconioses through four regular research grants and five subprojects within the Specialized Centers of Research (SCOR) program (a multi-disciplinary effort devoted to high priority problems such as pulmonary disease).

Black lung disease is initiated by the inhalation and retention of coal and other mine dusts in the lungs. A recent nationwide survey by the U.S. Public Health Service and the U.S. Bureau of Mines revealed that nearly 30 percent of working coal miners in the country have black lung disease.

A victim may be exposed to mine dusts 10 or more years before he is disabled or killed by the disease. During the interim, he experiences severe wheezing, coughing, shortness of breath, susceptibility to colds, and other respiratory infections such as tuberculosis. Heart failure is the most common cause of death. Autopsy examination of lung tissues shows that coal workers' pneumoconiosis involves five or more different disease processes.

Black lung disease begins when some of the inhaled dust particles become fixed into the walls of the small air passages (bronchioles) and sacs (alveoli), forming microscopic focal deposits called macules. A halo of emphysema (dead air space) soon begins to encircle each macule as the lung

(more)

tissue surrounding it is destroyed. Scar tissue formation (fibrosis) occurs between macules in some patients affecting large areas of the lung.

Chronic bronchitis and generalized forms of emphysema eventually develop and contribute to the shortness of breath and disability of the disease.

Finally, many victims suffer elevated blood pressure in the lungs (pulmonary hypertension). With this increased pressure, compensatory enlargement of the right side of the heart results.

Research shows that individuals with certain hereditary deficient conditions are more likely to develop black lung disease or have other health complications because of it. A particularly severe form of the disease may affect those lacking the enzyme alpha-1-antitrypsin. Workers who have the disease along with tuberculosis or rheumatoid arthritis are particularly prone to massive pulmonary fibrosis.

Because there is no known form of treatment that will arrest or reverse the course of black lung disease, therapy is aimed at relieving the symptoms and complications of the disease. A number of drugs and antibiotics are available to treat respiratory infections, dilate air passages, dissolve obstructive mucus secretions, and therefore lessen the severity of the disease. There has been some success, also, in preventing or controlling it.

In Great Britain, where coal workers' pneumoconiosis was first described, initiation of preventive measures more than 30 years ago has proved to be quite effective. Today mortality and disability have been cut in half.

Such control measures include reducing dust levels in the miners' working

(more)

environment, limiting the duration of exposure to dust, improving ventilation systems, and insisting on periodic X-ray examination and pulmonary function tests to detect the disease in its early stages. Other measures include the use of air filters, dust masks, and other equipment to collect dust or remove it from the atmosphere; rearranging work shifts to minimize individual exposure to dusty environments; use of dust monitoring systems.

Black lung disease research efforts are underway in an NHLI grant-supported study conducted by Richard L. Naeye, M.D., at the Pennsylvania State University, Hershey. The project, a combined clinical-epidemiological-pathological investigation of the disease processes that are involved, will include autopsy studies of coal workers, miners' wives, individuals not associated with the coal mining industry, and rural Pennsylvanians matched for age and race. The study has already correlated types and severities of disease manifestations with exposure to silica dust at different mine sites and in soft and hard coals.

Other projects by Dr. Naeye and NHLI grantees such as Edward A. Gaensler, M.D., have been conducted at Boston University School of Medicine. Findings have confirmed that respiratory impairment and functional disability cannot be determined accurately from chest X-rays, even though X-rays can accurately detect the presence and progression of dust deposits, fibrosis, and other tissue changes associated with the pneumoconiosis. This insight shows the composite nature of black lung disease and the fact that the severity of the disease's disorders can vary from patient to patient.

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Photo Feature

NIGMS FUNDS FIRST BURN TRAUMA CENTER

The Massachusetts General Hospital, Boston, will establish the first Burn Trauma Center to be funded by the National Institute of General Medical Sciences (NIGMS).

John F. Burke, M.D., a surgeon at the Hospital and chief of Shriners Burns Institute - Boston Unit, is principal investigator of the Center which will receive a three-year $789,504 grant to study various methods of treating serious burn injuries.

"The management of severe burns (30 percent total body surface) is still a critical problem," according to Emilie A. Black, M.D., acting deputy director, Clinical and Physiological Sciences Program, NIGMS. "Although there are effective means of handling the acute shock phase by judicious intravenous fluid replacement and other supportive measures, there has not been an appreciable decrease in overall mortality."

Dr. Black explained, "Rather there has been a shift in the time of death.

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Dr. Burke (right) discusses progress being made by a young burn victim at Massachusetts General Hospital with John D. Crawford, M.D., and Alia Y. Antoon, M.D., in front of a bacteria-controlled nursing environment. *(NIH Photo #1266)*

Many of those who survive the initial crisis die from overwhelming infections or from pulmonary or renal complications."

Additional burn research is conducted at some of the Trauma Research Centers that are supported by NIGMS.

University of Mississippi scientists are trying to reduce a burn victim's use of stored fuels by wrapping the injured portions in plastic. If energy expenditure can be reduced, the incidence of late burn deaths attributed to lack of food intake may be lowered. This NIGMS-supported study is at the medical center's Trauma Research Center. James D. Hardy, M.D., is principal investigator. Additional burn research at the Cincinnati General Hospital Trauma Research Center is directed by William A. Altemeier, M.D. (NIH Photo #1267)

Another method of treating burn patients is hydrotherapy, here shown underway at Albany Medical Center. (NIH Photo #1268)

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Medical News Tip

AMYOTROPHIC LATERAL SCLEROSIS--Amyotrophic lateral sclerosis, also known as ALS or motor neuron disease, is a progressive disease involving the nerve cells and their associated myelinating nerve tracts.

The first symptoms of ALS, which strikes men more often than women, include muscle weakness and wasting, and irregular muscle twitching of the upper extremities. The weakness is due to degeneration of the motor cells in the spinal cord and brain which should carry messages for action to the muscles.

The National Institute of Neurological Diseases and Stroke (NINDS) has directed extensive research relating to ALS for many years. At present, ALS studies are conducted at a center on Guam. The striking concentration of ALS among the Chamorro people of Guam has attracted the attention of the medical world since the early 1950's. Since 1956, NINDS has maintained a research center there devoted to the study of ALS, parkinsonism-dementia (a disease of the central nervous system that is unique to Guam), and other neurological disorders.

Since 1963, scientists have been exploring the possibility that ALS may be a slow virus infection. Ten years of study of the Guamanian population has indicated that the disease is not inherited in any known genetic pattern although more subtle genetic factors may play an indirect role. Also, investigations of the role of environmental factors have taken place in the Guam studies. Evidence is accumulating that exposure to the Guamanian environment does not increase a non-Chamorro's risk of developing ALS.

For additional information about the NINDS studies of ALS, contact: NINDS, Bldg. 31, Room 8A-03, Bethesda, MD 20014, Phone: (301) 496-5751.

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New Publication:
Pollen Allergy

Pollen allergies, commonly known as hay fever or rose fever, plague more than 13.5 million Americans each year.

Not all pollens (the male germ cells of plants) cause allergies, however three factors--the buoyancy, quantity, and chemical composition of the pollen--contribute to its importance as an allergen. The most common causes of pollen allergies are tree, grass, and weed pollens.

Usually occurring during childhood or early adulthood, symptoms develop after the allergenic pollen enters the nose. The symptoms of allergic rhinitis, the most frequent form of pollen allergy, include sneezing, nasal discharge, and congestion. More severe complications are sinusitis, asthma, and secondary infections.

Once an allergy is suspected, a patient may be referred to an allergist for testing of specific pollen allergies. The intracutaneous skin test--in which a diluted amount of the pollen is injected under the skin--and the scratch test are the present methods for detection of an allergy.

Scientists have not found a cure for allergic disease; however, treatment can often bring significant relief from symptoms. Environmental control, through air conditioning or avoidance of the location of a particularly troublesome pollen, medications, and "allergy shots" can be effective in bringing relief.

A new publication, *Pollen Allergy*, released by the National Institute of Allergy and Infectious Diseases (NIAID), explains the symptoms, types, detection, and treatment of pollen allergies.

Science writers can obtain a free copy of this publication from: NIAID, National Institutes of Health, Building 31, Room 7A-32, Bethesda, MD 20014, Phone: (301) 496-5717.

#

News Releases Issued

ACUPUNCTURE--Scientists will evaluate acupuncture for pain control in dentistry under a grant from the National Institute of Dental Research to the Anesthesia Laboratory of the Harvard Medical School at the Massachusetts General Hospital, Boston. With the aid of volunteers, the investigators, headed by Gene M. Smith, Ph.D., will compare pain control from acupuncture with traditional analgesics and anesthetics during various dental procedures and during experimentally-induced pain. Their studies should show whether males or females and certain age or racial groups are more susceptible to acupuncture and whether success varies among the participating acupuncturists. If some acupuncturists obtain better results than others, their techniques and approach will be studied more closely.

ASBESTOS WORKERS--The National Cancer Institute has awarded a contract to monitor 878 Tyler, Texas asbestos workers who are at excess risk of developing lung cancer and other asbestos-related diseases. The individuals in this demonstration project are all former employees of an asbestos plant in Tyler which operated from 1954 to 1972. The contract, with the Texas Chest Foundation/East Texas Chest Hospital at Tyler, is funded at $472,289 for the first two years. The Hospital will attempt to identify characteristics signalling the development of lung cancer which may lead to earlier detection of the disease in a population at high risk.

INFLUENZA RESEARCH--The National Institute of Allergy and Infectious Diseases has established an influenza research center at the Baylor College of Medicine, Houston, Texas. The center will serve as a national focus of research efforts to find answers to many of the puzzling questions surrounding influenza. The Baylor center, supported in the first year by a $463,102 contract, will be under the direction of Dr. Robert B. Couch. He and a team of investigators will set up studies designed to clarify pathogenic, epidemiologic, and immunologic aspects of influenza, evaluate licensed and experimental vaccines, and explore the potential of antiviral substances in preventing or treating the disease. The investigators will observe different population groups--preschool and school-age children, college students, family units, and the elderly--for extended periods of time.

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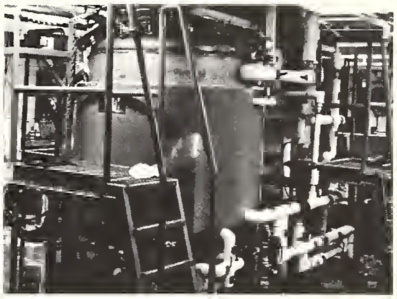
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Note to Subscribers

The answers to our annual Readership Survey are now tabulated. We are pleased with the 50 percent response rate and want to thank you for your assistance. Many of your comments and suggestions will be very useful to us in planning an improved news service.

We want to take this opportunity to answer certain questions raised by the survey and clarify certain points about *NFFN* articles:

1. Single copies of all New Publications mentioned in *NFFN* are available free to science writers and the general public by contacting the Institute listed in the article.

2. It is often impractical for us to list the addresses and telephone numbers of scientists mentioned in each issue. However, if you will contact us, we can usually supply this information or put you in contact with someone who can assist you.

3. In our June 25, 1974 issue, we ran an article entitled "Screening Tests Identify Cystic Fibrosis Carriers." If you are planning to use this material please keep in mind that the cilia assays used by Dr. Barbara Bowman are primarily research tools in their present stage of development. They are not currently practical for use in screening programs or prenatal diagnosis. These tests have led to the detection and partial purification of molecules which may be relevant to the pathogenesis of cystic fibrosis. When the molecules are isolated and characterized, these studies will hopefully lead to a definitive test and perhaps to the development of an improved approach to therapy.

The Editors

Research Advances

Voice-Print Analysis...

SOCIALLY-ISOLATED MONKEYS PRODUCE ABNORMAL SOUNDS

Voice-prints of rhesus monkeys separated at birth from their mothers and isolated from other monkeys, demonstrate some of the same abnormalities noted in sounds made by human patients with neurologic and psychotic disorders.

John D. Newman, Ph.D., and David Symmes, Ph.D., of the National Institute of Child Health and Human Development (NICHD), report this finding from their studies of two male and two female rhesus macaque monkeys deprived of physical contact with other monkeys from birth and minimally handled by human attendants. The animals were raised in separate incubators in the same room until about one month of age and then transferred to individual cages where they could see and hear, but not touch, other rhesus macaques of all ages.

The investigators made video tape recordings of these animals at nine, 12, 16, and 24 months of age and analyzed the vocalizations with a sound spectrograph. Three mother-reared rhesus macaque monkeys (two males and a female) served as controls.

Drs. Newman and Symmes recorded several kinds of vocalizations. Pant-threats, geckers, squeaks, and screeches--calls generally associated with arousing circumstances such as the entry of the observer into the room or the capture of the monkey--were structually similar in both groups.

However, the investigators report finding structural abnormalities in the frequent clear calls (non-noisy) or "coos" of the socially-deprived

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monkeys as distinguished from the louder squeaks or screeches. (This type of call is generally given by infants deserted by their mothers and by older monkeys when separated from their social group.)

More than 90 percent of the clear calls recorded from the deprived animals during the observation sessions had several abnormal structural features, including abrupt pitch changes, harmonic emphasis shifts, breaks in the continuity of sound, lack of inflection, and a "hollowness" of sound.

Although all of the deprived monkeys produced sounds with more than one of these structural abnormalities, each monkey had a distinctive set of abnormalities which characterized most of its clear calls at every age in the test period. These abnormal vocalizations of the isolated monkeys persisted through the subjects' second year of life.

The vocal abnormalities described by Drs. Newman and Symmes have close counterparts in human vocal pathology. Voice-prints obtained in studies of human adults with mental illness and of brain-damaged infants demonstrate comparable pattern of abnormalities. Abrupt pitch changes, vocal discontinuities, lack of inflection, abnormally long duration, and structural disorganization were reported in these previous investigations as symptomatic of human neurologic and psychotic disorders.

One exception to the abnormal vocalizations in the present study was observed in several instances involving an external disturbance, such as when the deprived monkeys were being held or when an observer was nearby. On these rare occasions, the deprived monkeys gave "coos" indistinguishable from those of the control group. "Coos from the control monkeys, including

(more)

those heard during brief separations of these animals from their mothers, had a smooth, gradually-inflected harmonic structure and were unbroken in sound.

Spectrographic descriptions of sound made by socially active macaques in captivity have been reported previously by researchers in England. However, the present report is believed to be the first analysis of voice pathology of primates socially isolated since birth.

Drs. Newman and Symmes, of the NICHD Behavioral Biology Branch, report their findings in *Developmental Psychobiology*, July 1974.

#

TRAUMA--Head injuries, respiratory failure, problems of wound healing, infection, abnormal blood function with impaired oxygen delivery, and bleeding are complications of trauma, according to the National Institutes of Health.

CENTRAL NERVOUS SYSTEM--At birth, low birth weight infants, infants of diabetic mothers, and infants with adrenal insufficiency cannot maintain an adequate level of blood glucose for central nervous system function, according to the National Institutes of Health.

Research Advances

VACCINE PREVENTS STREPTOCOCCAL COLONIZATION AND INFECTION

Prevention of colonization of the throat by Group A, Type I streptococci, the organism which causes strep throat, is an important advantage gained by a new immunization route for a vaccine developed by National Institute of Allergy and Infectious Diseases (NIAID)-supported scientists at the University of Chicago and the University of Florida.

The vaccine, which was known to prevent streptococci respiratory infections when injected, was recently shown to have this added capability when sprayed into the nostrils and throat. If subsequent clinical trials confirm this observation, the researchers feel that they can reduce the number of potential carriers, prevent the transmission of the organism, and thus greatly diminish the community reservoir of infection.

Strep infections, in particular those caused by Group A streptococci, are the most common human bacterial diseases. Initial strep infections are often mild, but dangerous because they are sometimes followed by fatal diseases. Because sore throats occur frequently in school-age children, strep pharyngitis which can develop into rheumatic fever with subsequent permanent heart damage often goes undiagnosed.

Penicillin and other antibiotics can cure the initial strep infection and prevent the development of subsequent disease. However, a vaccine that could decrease the number of strep carriers in the population could significantly curtail the spread of the organism with its associated dangers.

The NIAID grantees and contractors, Eugene Fox, Ph.D., Albert Dorfman, M.D., Ph.D., and Masako K. Wittner of the La Rabida Children's Hospital and

(more)

Research Center and the University of Chicago; and Robert H. Waldman, M.D., and Stuart M. Polly, M.D., of the University of Florida School of Medicine, prepared the vaccine from soluble M protein, Type I. M protein, the outermost layer of the strep cell wall, is the major virulent factor of the organism. Antibodies developed against the M protein in natural infections, although type-specific, confer long-lasting immunity.

The investigators administered three monthly doses of vaccine via nasal and throat sprays to 21 volunteers at the University of Florida, while 23 subjects received a placebo of sterile saline. Both groups were challenged with live Group A, Type I streptococcus 30-50 days after their final dose.

As a result, five of the vaccinees and 19 of 23 controls developed positive strep cultures. The investigators report that five of the vaccinees were obviously ill and one was questionably so, while 11 controls were obviously ill and six were questionably so. Each patient received penicillin treatment. The investigators say that lack of clinical illness in most of the volunteers indicates that colonization in these individuals did not take place.

Although only a few of the vaccinees had detectable antibodies, the extent of the protection was similar to that obtained when the vaccine is administered by injection. This lack of circulating antibody was not unusual since antibodies elicited by application of an antigen to mucous surfaces are localized in that surface. Further studies must be done to determine if the intranasal vaccine can produce a long-lasting immunity.

This work was presented at the 75th anniversary meeting of the American Society for Microbiology in Chicago on May 15, 1974.

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Research Advances

In The Literature:
Antimicrobial Agents and Chemotherapy, February 1974

NEW DRUG SHOWS PROMISE IN TREATMENT OF GONORRHEA--A single oral dose of a new semisynthetic penicillin--called amoxicillin--seems to be as effective in the treatment of gonorrhea as the recommended Public Health Service regimen of ampicillin and probenicid.

In a collaborative study in Seattle, scientists supported by the National Institute of Allergy and Infectious Diseases and other sources evaluated these drugs. Their results indicate that amoxicillin, if given in combination with probenicid or if prescribed in two divided doses, four to five hours apart, might be even more effective than comparable doses of ampicillin.

The discovery and evaluation of new and more effective drugs is of vital importance in controlling the current epidemic of gonorrhea, particularly in light of certain therapeutic problems which have developed. The capability of *Neisseria gonorrhoeae,* the infectious organism, to develop resistance to current antibiotics necessitates a constant search for new ones. Drug allergies and the failure of the one-dose regimen to cure some patients further complicate the treatment of this venereal disease.

In assessing the efficacy of amoxicillin as compared to ampicillin-probenicid, the Seattle scientists--Walter Karney, M.D. of the University of Washington School of Medicine, Marvin Turck, M.D., of the Harborview Medical Center, and King K. Holmes, M.D. of the Public Health Service Hospital--treated 114 men and women with uncomplicated gonorrhea. In patients with genital or anal infection, 95.8 percent who received a single dose of 3.0 g

(more)

of oral amoxicillin were cured while 97.3 percent who received an oral dose of 3.5 g of ampicillin plus 1.0 g of probenicid were cured. A significant finding was that the concomitant oropharyngeal infection in three patients was not cured by the ampicillin-probenicid regimen, even though the anogenital cultures were negative for these patients.

Members of the Seattle group suggest that the key to effective dosage may depend upon the length of time that the drug is concentrated in the serum. Prolongation of concentration above a certain level for up to 12 hours may be necessary to cure gonorrhea. If this can be achieved using a single drug, such as amoxicillin, it would be preferable to utilizing two potential allergenic drugs, ampicillin and probenicid.

#

TRAUMA--In trauma treatment, oxygen tensions in the healing wound can now be measured and the status of the wound assessed by its oxygen consumption. The greater the oxygen consumption, the healthier the wound, according to the National Institutes of Health.

Photo Feature

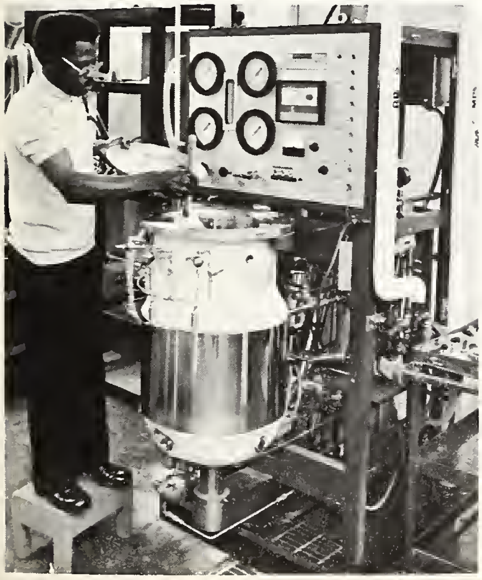
Bacteria, Viruses, Enzymes...

NIAMDD PILOT PLANT AIDS BASIC RESEARCH

The Pilot Plant at the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD) assures a continuing supply of bacteria, bacteriophages, viruses, and enzymes in large quantities for NIH researchers.

The Plant is particularly valuable to scientists who require large amounts of source material to isolate small amounts of biologically interesting compounds. This source material--of human, animal, or plant origin--can be in the form of tissue culture or bacteria. The desired material could be an enzyme, drug, vitamin, nucleic acid, virus, or protein. When a scientist schedules a run, he specifies the growth conditions according to the parameters developed in his own laboratory.

The Pilot Plant, operated by David Rogerson with the aid of Douglas Johnson, Clark Collins, and Jim Oden, is part of the NIAMDD Laboratory of Nutrition and Endocrinology. Herbert A. Sober, Ph.D., is chief of the Laboratory.

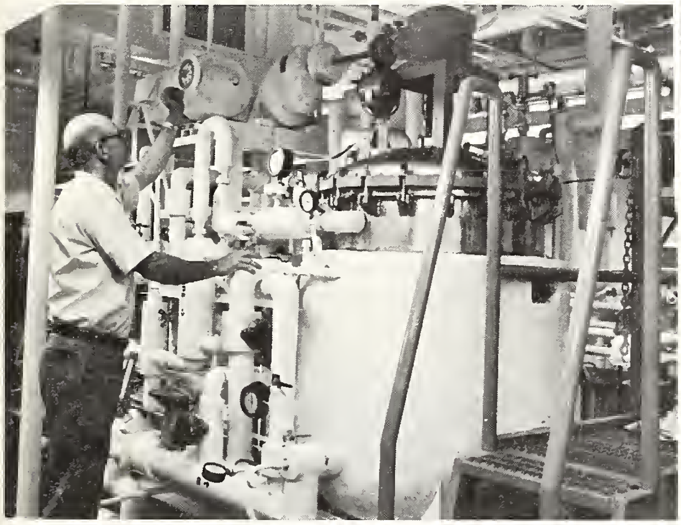


The equipment in the Plant is scrubbed manually by Douglas Johnson and sterilized by steam to prevent contamination of the organism to be processed. A small sample is tested for purity and then a sufficient quantity (usually ten liters) is inoculated into a 300-liter or 1000-liter fermenter. (NIH Photo #1269)

(more)

Pilot Plant (Cont'd)

To monitor the progress of organism growth, Clark Collins draws a sample periodically and tests it for light density (right). The growth rate is then adjusted by David Rogerson through controls on the fermenter to meet the specifications for the procedure (below). (NIH Photos #1270, 1271)



When the desired growth level is reached, the organisms are moved from fermenters into continuous centrifuges from which they are harvested. The desired material might be prepared in the form of a solid bacterial paste that is scraped from centrifuge bowls (as David Rogerson does here), or in a liquid form that is drawn from a tap. (NIH Photo #1272)

#

Photo Feature

Disease Carriers...

FLORIDA LABORATORY STUDIES MOSQUITOES

The disease-transmitting potential of arthropods, especially mosquitoes and sandflies, is under study at the Florida Medical Entomology Laboratory, Vero Beach.

The research, supported in part by the National Institute of Allergy and Infectious Diseases, begins with studies of insects in natural settings. Such field investigations establish what observations need to be verified through laboratory experiments.

"Improved methods of disease control should result from thorough studies of the ecology, ethology, physiology, and biochemistry of certain insects," according to Maurice W. Provost, Ph.D., administrator of the Laboratory.

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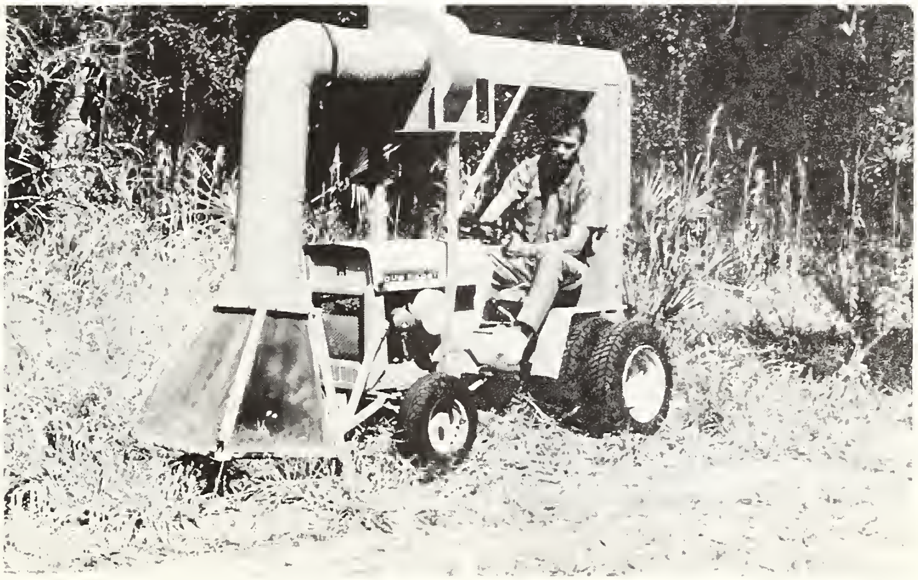
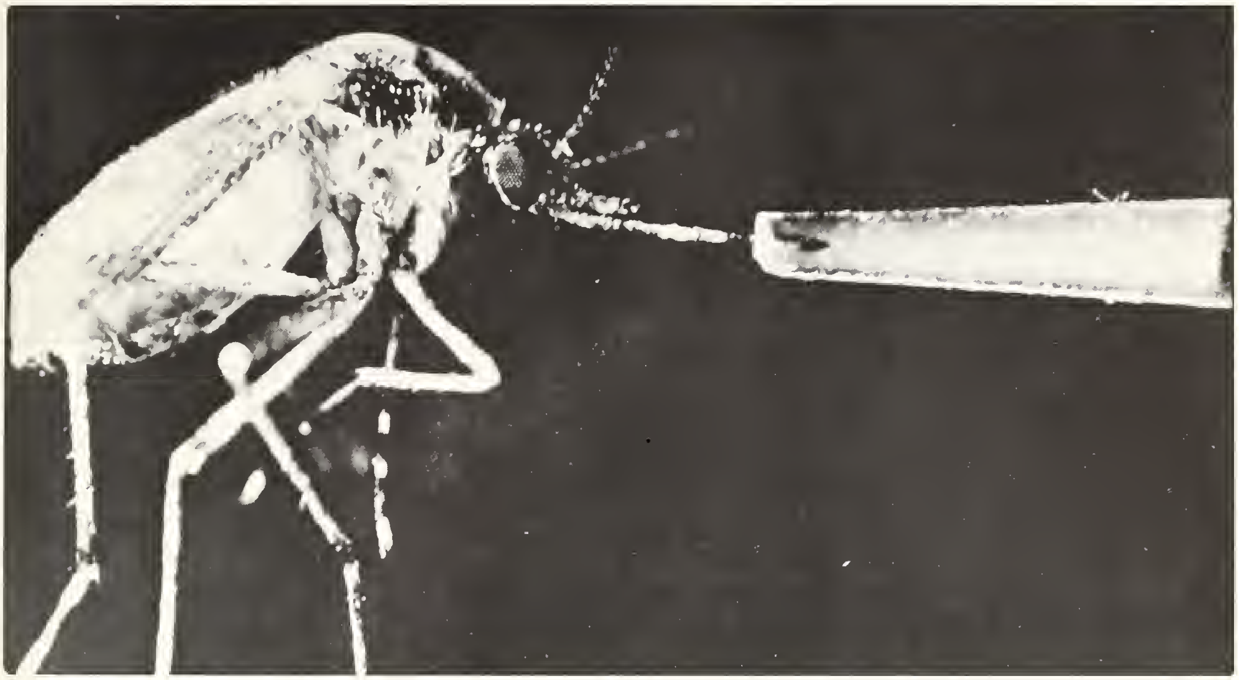


This small tractor has been fitted with a special attachment developed at the laboratory to facilitate finding mosquitoes and capturing them in daylight. An aspirator skims the area just above the ground, disturbs mosquitoes that are resting in leaf litter, and draws them into "protective custody" to await laboratory studies. (NIH Photo #1273)

Mosquitoes (Cont'd)



Laboratory scientists use special miniature instruments to study the blood that a mosquito has drawn and the way a mosquito "processes" the blood. (NIH Photo #1274)

In a salt marsh, mosquito-rearing swales can yield as many as 500,000 mosquitoes per swale. (NIH Photo #1275)

A scientist observes and records mosquito activity in a research aviary. One finding that resulted from such observation is that mosquitoes bite birds that are most easily available rather than consistently seeking a specific bird family. (NIH Photo #1276)

#

Medical News Tip

ORGAN TRANSPLANT IMMUNOLOGY--In the fall of 1964, the National Institute of Allergy and Infectious Diseases (NIAID) established a collaborative program in immunology to provide information needed by investigators working in the field of organ transplantation. Scientists had just begun to use drugs to suppress the body's tendency to reject foreign tissue and the transplantation of organs has thus become a therapeutic possibility for persons with kidney and other serious diseases.

The first contract awarded under the program resulted in the development of a laboratory technique which is now the standard procedure in tissue typing. The same contract supported the development of the NIH typing tray, a multiple serum syringe, and a transport system which permits mailing blood samples for typing. Computer programs for analysis of typing data were also developed.

A contract awarded in 1966 led to the discovery of the mixed lymphocyte culture (MLC) reaction which was then used by NIAID grantees in further research which resulted in a second test for histocompatibility.

Using procedures developed by NIH intramural and grantee scientists, an industrial laboratory, funded by NIAID contract, developed large-scale processes for the production of functionally active components of human complement, an important participant in the immune response.

For additional information about these and other NIAID advances in the field of transplant immunology, contact: NIAID, Bldg. 31, Room 7A-32, Bethesda, MD 20014, Phone (301) 496-5717.

#

New Publications:
Facts About Mongolism for Women Over 35
Antenatal Diagnosis and Down's Syndrome

Mongolism, or Down's syndrome, is characterized by various mental and physical abnormalities and by the presence of an extra chromosome. This extra genetic material usually emerges during the development of the egg or sperm or during fertilization.

While the cause of mongolism is yet unknown, three genetic types have been identified: Trisomy 21 (where there are three chromosomes instead of two in chromosome 21), Translocation (in which a chromosome breaks and becomes attached to another), and Mosaicism (a rare type occurring when an individual has cells with different chromosome counts). Trisomy 21 occurs in about 95 percent of all cases of mongolism.

The chances of bearing a child with Down's syndrome rise with maternal age, increasing sharply for women over 35 and even more for those over 40 years of age. The chance of a woman under 30 years old bearing a child with mongolism is one in 1500, while the chance of a woman between the ages of 40 and 44 having such a child is one in 100.

Two new publications, *Facts About Mongolism for Women Over 35*, and *Antenatal Diagnosis and Down's Syndrome*, will be released by the National Institute of Child Health and Human Development (NICHD) in conjunction with a briefing on the subject. The first pamphlet explains the types, characteristics, detection, and risks of Down's syndrome; the second is written to aid doctors and other health professionals who must advise patients about the subject.

Science writers can obtain a free copy of either publication from: NICHD, Landow Building, Room A-804, Bethesda, MD 20014, Phone: (301) 496-5133.

#

News Releases Issued

ECMO--The National Heart and Lung Institute is launching a three-year $6 million collaborative program involving nine institutions which will test the therapeutic efficacy of an external device--the extracorporeal membrane oxygenator (ECMO)--that provides oxygen to the blood in patients with acute respiratory failure. The ECMO systems to be used in the study have been developed in animal studies to the point where they provide long-term (1-2 weeks) support to the lung without serious blood damage because the circulating blood and external oxygen are separated by a thin membrane. Recently, clinical experience has shown that these membrane oxygenators can be used successfully to provide partial respiratory support for patients with acute respiratory failure. During this past year, at least six ECMO-treated patients have survived acute respiratory failure. The program will compare patients treated by conventional, lung-ventilating modes of therapy with those treated by a combination of the conventional and ECMO therapies.

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August 10, 1974

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NEWS & FEATURES From NIH August 10, 1974

Brief Report
Research Advances

Cause of Hepatitis B...

ADDITIONAL DATA SUPPORT DANE PARTICLE HYPOTHESIS

NIH-supported scientists, following up their earlier discovery of a specific enzyme associated with hepatitis B, have now reported that the transient nature of this enzyme in the blood and the time at which its peak activity is found resemble the course of other viral diseases. This supports the hypothesis that the Dane particle, which contains this enzyme, is the virus of hepatitis B.

In their latest studies of this enzyme (DNA polymerase) specific for hepatitis B, Paul M. Kaplan, Ph.D., and John L. Gerin, Ph.D., of the National Institute of Allergy and Infectious Diseases-supported Rockville Laboratory of the Oak Ridge Molecular Anatomy (MAN) Program; and Harvey J. Alter, M.D., of the NIH Blood Bank, collected plasma samples from multiply-transfused patients at frequent intervals after surgery. The investigators analyzed the samples not only for the presence of the DNA-polymerase but also for hepatitis B antigen, for antibody to the antigen, and for the presence of serum glutamic-pyruvic transaminase (SGPT)--a substance which indicates liver damage.

Seven of nine patients who developed post-transfusion hepatitis B, as indicated by the presence of hepatitis B antigen and elevated SGPT, had detectable hepatitis B-specific DNA polymerase activity in their plasma during acute infection. In all cases, this preceded signs of liver damage and appeared slightly after the antigen was first detected. Polymerase activity was not found in the plasma of a patient with hepatitis B-negative

(more)

post-transfusion hepatitis nor in four persons without hepatitis who served as controls.

On the basis of their research, the NIH scientists believe that the DNA polymerase activity is a measure of the actual level of infectious virus, since this activity is specific for the presence of Dane particles, the suspect virus.

The investigators published the results of the present study in *Nature*, June 21, 1974. A report of the initial finding appeared in the *Journal of Virology*, November 1973 and was reported in *NFFN*, November 25, 1973.

#

CHOLESTEROL--Cholesterol, a fatty alcohol, or sterol, is found in all animal tissues and is especially abundant in the fat and fatty products of milk, eggs,and organ meats. There is none in vegetables or their native fats and oils. The average American diet supplies some 500-700 milligrams per day. The rest of the cholesterol in the blood is made in the body, mostly by the liver , according to the National Institutes of Health.

Research Advances

In The Literature:
The Journal of Experimental Medicine, February 1974

VIRUS, HEREDITY INTERACT TO PRODUCE DIABETES IN MICE--Genetic factors have been shown to influence the occurrence of virus-induced diabetes in mice. This finding reported by National Institute of Allergy and Infectious Diseases grantees may aid understanding of the causes of human diabetes, particularly the juvenile type.

There has been substantial evidence to support the theory that heredity plays a role in the development of human diabetes. Also, evidence has indicated that certain viruses may provoke onset of the disease, although only a small fraction of infected individuals are so affected. Since genetic factors influence susceptibility to viruses, such influence on the response to diabetes-causing viruses may be one mechanism by which heredity affects the occurrence of diabetes.

To examine this proposition, scientists at the University of Vermont College of Medicine undertook to study the effects of a diabetes-inducing virus in mice of varying genetic constitutions. The agent, encephalomyocarditis or EMC virus, resembles viruses of the type implicated in diabetes causation in man and produces a disease in mice which exhibits many features of human juvenile-type diabetes.

John E. Craighead, M.D., and Duncan A. Higgins studied two strains of mice (DBA/2 and C3H) selected after a preliminary survey of the responses of various strains to EMC virus infection. Mice of both strains, when inoculated with the virus, developed systemic infections, and, in the course of the infections, virus multiplied to a similar extent in animals of both types.

(more)

However, mortality was greater among infected DBA/2 mice, and blood tests revealed abnormally high levels of sugar in these animals. Blood sugar levels in the C3H mice, however, remained in the normal range.

Microscope studies of the insulin-producing portions of the pancreas of infected animals showed marked abnormalities in DBA/2 mice, in contrast to near-normal appearance in C3H individuals. Members of the two strains also differed in their production of neutralizing antibody against EMC virus, with the DBA/2 mice making far more antibody than did C3H animals.

In addition to the original mouse strains, the investigators studied progeny of a cross between these strains and progeny of backcrosses of the resultant hybrids with mice of the parent strains. Data obtained suggest that production of diabetes by EMC virus is influenced not by a single genetic factor, but rather by several genes acting in concert.

The nature of the hereditary factors influencing development of diabetes in EMC virus-infected mice remains unknown. Observed differences between strains might reflect something as general as inherited variations in metabolism or as specific as genetic differences in susceptibility of insulin-producing cells. Regardless of mechanism, however, the present study furnishes a model of viral induction of diabetes limited to genetically susceptible individuals.

#

Research Advances

In Rhesus Monkeys...

RESEARCHERS PRODUCE EXPERIMENTAL GLAUCOMA

National Eye Institute (NEI) scientists have developed what appears to be the first suitable animal model for studying the effects of chronic elevation of pressure within the eye, a characteristic of glaucoma.

Douglas E. Gaasterland, M.D., of the NEI Clinical Branch, and Carl Kupfer, M.D., Institute director, have developed a method for inducing changes in the eye of the rhesus monkey which closely resemble those observed in human chronic, open-angle glaucoma, the most common form of the disease.

While research has made it possible to treat most cases of this type of glaucoma medically, the ultimate goal is to find a means of preventing this major cause of blindness. To approach this objective, researchers must better understand how glaucoma actually causes loss of vision. Progress, however, has been delayed by the lack of an appropriate animal model for the disease.

Glaucoma results when an obstruction in the outflow of a fluid, aqueous humor, leads to increased pressure within the eye, with subsequent damage to the optic nerve and loss of vision. In chronic, open-angle glaucoma, there is no gross obstruction within the aqueous outflow channels, but a blockage does exist, probably at a sub-microscopic level.

To produce sustained, elevated pressure, the researchers used argon laser photocoagulation. In this procedure, an intense beam of fine, but brilliant, blue-green light is directed into the eye of the anesthetized

(more)

monkey and aimed at the aqueous outflow channels. The energy of the laser light beam causes minute burns. Then, healing from these burns creates an obstruction in the outflow channel which causes the pressure in the eye to increase.

Drs. Gaasterland and Kupfer report that repeated laser applications cause a sustained pressure elevation and a marked reduction in the outflow facility of the aqueous fluid from the eye. Retinal and optic nerve changes, similar to those seen in human chronic, open-angle glaucoma, developed.

According to the scientists, the experimental ocular hypertension produced differs from previous models in several important ways. First, the sustained elevation of pressure is produced by the use of a noninvasive technique. Second, the mild to moderate initial inflammation caused by the photocoagulation is temporary, lasting usually less than two weeks. Third, the primary alteration induced in the eye is localized in the region of the aqueous humor outflow pathways.

"This model provides us with a tool for studying why and how glaucoma causes visual loss," Dr. Gaasterland explained. "It allows us to conduct investigations that cannot be done in humans, but are necessary to our understanding of the effects of glaucoma in patients."

The investigators point out that there are a number of previous models of experimental, ocular hypertension. However, each type has been associated with either a generalized damage to the eye or a pressure rise of insufficient duration to cause selective loss of retinal ganglion cells, a degenerative change associated with ocular hypertension that is required to make a histopathologic diagnosis of glaucoma.

(more)

Glaucoma (Cont'd)

Drs. Gaasterland and Kupfer conclude that the experimental ocular hypertension they have described is glaucoma because of the development of cupping of the optic nervehead and the selective loss of retinal ganglion cells. Further research will be needed to demonstrate conclusively the suitability of the monkey model for chronic, open-angle glaucoma. However, the investigators expect that their new experimental method will significantly enhance research efforts to understand better the basic processes underlying glaucoma. Such information will greatly facilitate research directed toward finding means of curing or preventing this disease.

A full report of these findings is published in *Investigative Ophthalmology*, June 1974.

#

PARKINSON'S DISEASE--Parkinson's disease is a progressive neurological disorder affecting the brain center responsible for control and regulation of movement, according to the National Institutes of Health.

GOUT--Gout is the most treatable of the common joint disorders, according to the National Institutes of Health.

Photo Feature

GRANTEES TO DEVELOP MATERIALS FOR USE IN ARTIFICIAL ORGANS

Scientists at Case Western Reserve University (CWRU), Cleveland, hope to solve some of the problems associated with artificial organs as part of a project supported by the National Heart and Lung Institute.

The five-year program is supported by a $1.6 million grant for direct costs. The goal of the program is the production of biomedical polymers as the basis for synthetic materials for artificial arteries, veins, and possibly artificial hearts.

Work on such materials began four years ago at the school. The materials, made from amino acids, are dissolved in solvents and a sheet is produced by evaporation. Samples of the polymers have been implanted in rats for up to a year and were found to be well tolerated.

The project will deal with the synthesis and design of new materials, testing and evaluation of the physical properties, and biological testing with blood clotting and tissue culture tests.

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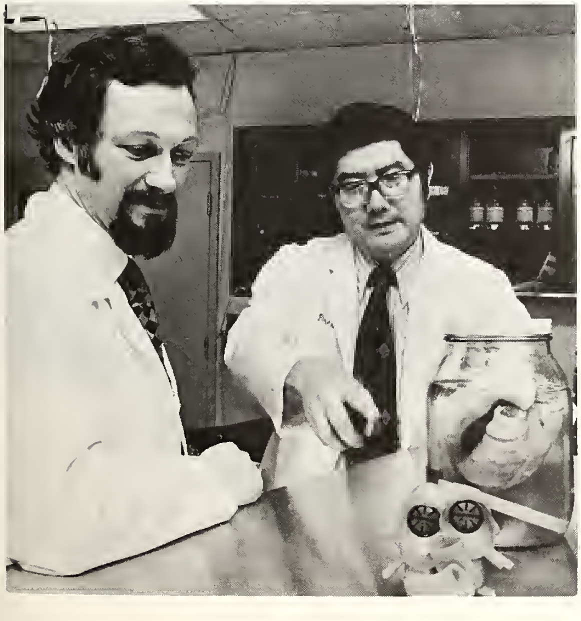

Dr. Walton(left) will be involved in the synthesis and design of the new materials and in the testing and evaluation of their physical properties. Yukihiko Nosé, CWRU adjunct professor of Biomedical Engineering and head of the Department of Artificial Organs of the Cleveland Clinic, will be involved in testing the whole blood compatibility of the bioplastics in vitro *and, eventually, in implanting the newly-developed materials in a prototype of an artificial heart. (NIH Photo # 1277)*

Artificial Materials (Cont'd)

The scientists will be concerned primarily with blood clotting and those factors which cause most substances to induce clotting when placed in the body in contact with the blood stream.

Alan G. Walton, Ph.D., professor of Macromolecular Science, is director of the program. Dr. Walton and Donald F. Gibbons, Ph.D. , professors of Biomedical Engineering, are co-principal investigators for the project.

A team of 16 people, drawn from the University's School of Medicine, the Cleveland Clinic, and the Case Institute of Technology, will work on the project.

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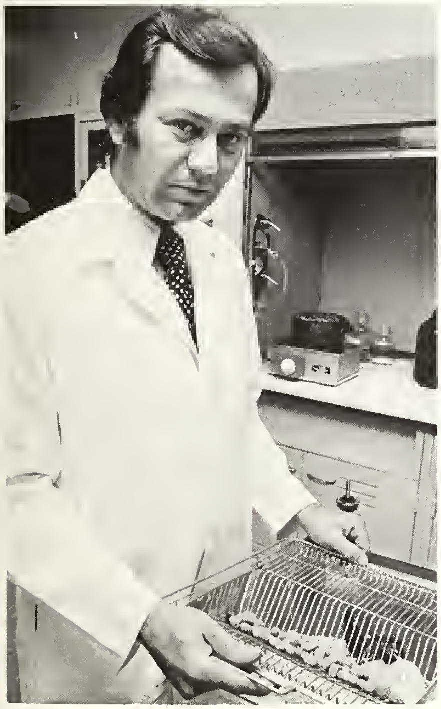

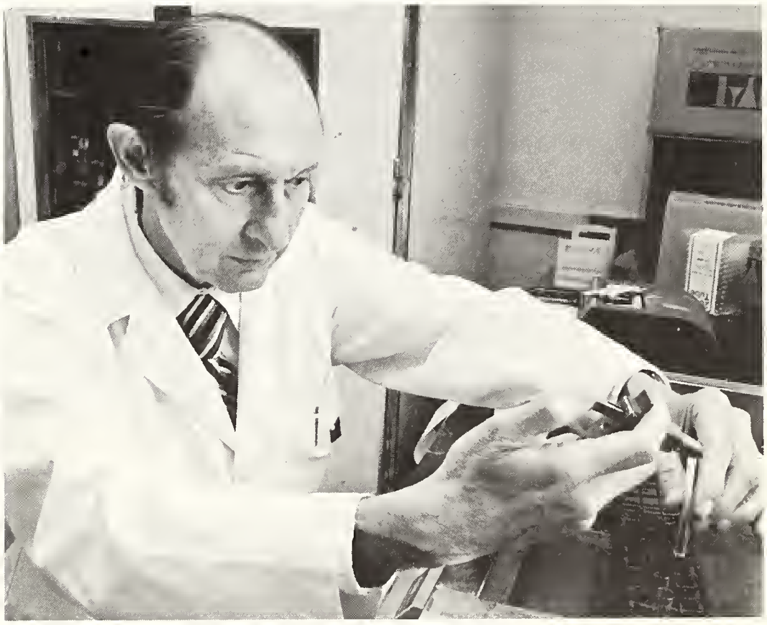

Robert L. Martin, M.D., assistant professor of Pathology at the School of Medicine and director of Clinical Laboratories at University Hospitals of Cleveland (left), will test the newly developed bioplastic materials for biological stability and possible inflammatory, carcinogenic, and reactive properties. Robert Cook, M.D., Ph.D., and Oscar Sudilovsky, M.D., assistant professors of Pathology, will collaborate with Dr. Martin. (NIH Photo # 1278) Oscar M. Ratnoff, M.D., professor of Medicine at the School of Medicine (below) will investigate whether the use of the new biomaterials might be complicated by thrombosis. Dr. Ratnoff, co-director of the Division of Hematology at the University Hospitals of Cleveland, is an authority on intrinsic clotting mechanisms. (NIH Photo #1279)

NEWS & FEATURES From NIH August 10, 1974

News Feature

VACCINATION MAY ONE DAY PREVENT TOOTH DECAY

Vaccination may one day prove to be a simple means of preventing dental decay. According to William Bowen, Ph.D., of the National Institute of Dental Research (NIDR) National Caries Program, the concept of adopting an immunological approach to controlling caries is not "far fetched", even though the tissue affected by the disease, enamel, is not in direct contact with the immunological system of the body.

Dental enamel, an essentially unreactive tissue, is colonized constantly by acid-producing bacteria, which under suitable conditions initiate progressive demineralization and cavitation. The areas most often involved, the crowns of the teeth, are physically isolated from the most common source of antibodies, the blood-vascular system. Therefore, an attack of caries, unlike most infectious diseases, does not confer resistance to a subsequent attack, at least so far as now known.

In addition, the infection has not been shown to engender the characteristic serum antibody response. Since the tooth is bathed in saliva, immunization through the secretory system would appear to offer a better approach than the blood-vascular system.

The search for a caries vaccine goes back many years. On the assumption that lactobacilli were the cause of dental caries, previous investigators prepared a vaccine of various strains of lactobacillus acidophilus and injected the preparation into humans. While a reduction in the number of lactobacilli was reported, no information was developed on the effect the vaccine may have had on the development of tooth decay. Epidemiological investigations

(more)

in England and the United States have indicated that a relationship may exist between the prevalence of dental caries and the levels of immunoglobulins and antibodies in saliva.

The essential factor in the pathogenesis of dental caries is that a susceptible tooth must be colonized by cariogenic microorganisms. The initial stage in this colonization leading to the formation of dental plaque is the adsorption of protein from saliva to form a pellicle on the surface of the tooth. Microorganisms suspected in the cause of tooth decay attach themselves to this layer of pellicle. The plaque increases in bulk through the growth of these microorganisms and their formation of sticky dextran and levan from carbohydrate metabolism.

A vaccine against dental decay may prevent dental caries through several possible mechanisms. Following vaccination, antibody may enter the mouth through the salivary glands and through the gingival tissues. The antibody could combine with microorganisms and prevent them from colonizing the tooth surface. Antibody may also prevent the formation of dextran and levan by preventing the interaction of bacterial enzymes and carbohydrates. A third possibility derives from the fact that microorganisms covered by a layer of antibody are very susceptible to destruction, or phagocytosis, by white blood cells. Significant numbers of white blood cells migrate into the mouth and are commonly found in saliva. This may lead to a reduction in the number of decay-causing bacteria.

Rodents have been successfully vaccinated against caries using both dextran-sucrase and levan-sucrase. However, the monkey offers several advantages as an experimental animal, since it can be subjected to procedures

(more)

which are difficult to carry out in the rodent. The monkey, when fed a human diet, develops carious lesions which clinically, radiographically, and histologically cannot be distinguished from those which occur in humans. Also, antibodies produced against human immunoglobulins react with those of the primate.

In studies in London, scientists succeeded in reducing the number and severity of decay lesions in monkeys by intravenous injection of live *Streptococcus mutans*. However, it is possible that more effective results can be obtained from using the secretory as well as the serum system.

This approach has been made at the State University of New York at Buffalo by NIDR grantees. Injections of killed *S. mutans* were made into the ducts of the parotid salivary gland of anesthetized monkeys. The vaccine stimulated production of salivary antibodies against the decay-causing *S. mutans* and dramatically reduced the amount of this organism in dental plaque.

Although this achievement is encouraging, more work remains to be done before a vaccine can be tested in man. First, it must be proven that a vaccine against only one organism will decrease decay significantly and that it is safe. Because injections into salivary glands are not without pain and risk of infection, scientists are also looking for alternate routes of administration.

#

Photo Feature

STANFORD "HOTEL INSOMNIA" TO STUDY THE SLEEPLESS

A dormitory equipped with electroencephalograph machines will provide bedrooms for people who can't sleep as part of a National Institute of Neurological Diseases and Stroke-supported research project at the Stanford University "Hotel Insomnia."

Recent studies have already revealed several previously unsuspected causes of insomnia. One such example is a peculiar condition called nocturnal myoclonus, in which the muscles of the anterior calf twitch continuously only during sleep and eventually awaken the sleeper. Approximately one-fourth of the insomniacs tested in the past few months at Stanford exhibited this symptom.

Another problem to be investigated at the Stanford Sleep Disorders Clinic is sleep apnea insomnia, where patients stop breathing for repeated intervals and must awaken to resume normal respiration.

These and other causes can be identified only by extensive observation and brain wave analysis in both insomniacs and normal subjects. Once the cause can be detected, it may be treated to reduce or eliminate the sleeper's problem.

#

William C. Dement, M.D., Ph.D., director of the Stanford Sleep Disorders Clinic, checks the equipment which records the activity of a sleeping subject at "Hotel Insomnia." (NIH Photo #1280)

Medical News Tip

REGULATION OF GENE ACTIVITY--Robert T. Simpson, M.D., Ph.D., of the National Institute of Arthritis, Metabolism, and Digestive Diseases has described new evidence that may explain how genes "turn on" and "turn off" in living cells.

Dr. Simpson's findings suggest that genes (composed primarily of the hereditary chemical DNA) are actively turned on and able to operate when the histone (protein) bonds which are attached to the DNA loosen. By contrast, when histones are tightly attached to the genetic material, the DNA becomes folded or "supercoiled" and virtually paralyzed and unable to generate the life functions.

For his studies, Dr. Simpson employed chromatin (DNA linked to histone protein) as well as protein-free DNA. Evidence of whether or not the DNA's were genetically active or "turned on" was provided by their ability to produce a sister chemical, RNA, after adding a "priming" enzyme.

Scientists have known for years that some genes may turn on only once in the lifetime of a cell or organism, providing the critical blueprint needed for a specific chemical product and then resuming complete inactivity. Since all life processes are controlled by gene activity and regulation, an understanding of gene mechanisms is a major scientific priority.

Dr. Simpson's findings appear in the July 1974 issue of *Proceedings of the National Academy of Sciences* and the recently published "Current Topics in Biochemistry--1973," Academic Press, 1974.

For additional information about this work, contact *NFFN*.

#

New Publication: *Interferon*

Interferon, a protein produced by body cells in response to attack by viruses and some other intracellular parasites, was once thought of exclusively as an antiviral weapon. However, results of recent research have indicated that interferon--in animals--is also effective against certain protozoal parasitic infections,such as malaria, and against tumors.

Scientific interest in interferon is still focused most sharply on its ability to assist in an animal's recovery from viral infections. Control of the wide spectrum of human illnesses caused by viruses has long been the goal of medical research and is a special concern of the National Institute of Allergy and Infectious Diseases (NIAID).

According to the Institute's revised publication, *Interferon,* this goal has been reached for some diseases through the development of vaccines. The publication discusses the discovery of interferon, explains how interferon works, and highlights research done through the NIAID Collaborative Program whcih has awarded a number of contracts for specific studies of interferon and interferon inducers through its Antiviral Substances Program. These investigations are part of the Institute's targeted research effort on antiviral drugs.

By providing a broad base for interferon research, NIAID hopes to hasten the day when clinical use of interferon may become practical.

Science writers can obtain a free copy of this publication from:

NIAID
Building 31, Room 7A-32
Bethesda, MD 20014
Phone: (301) 496-5717

#

News Releases Issued

MARC PROGRAM--The MARC Program of the National Institute of General Medical Sciences has awarded $3,214,880 in health scientist training grants to graduate institutions serving predominantly minority group students. MARC, the Minority Access to Research Careers program, was started two years ago by NIH to help minority schools expand their biomedical research and teaching capabilities relevant to the accomplishment of health goals. Four of the new grants were made to the Howard University College of Medicine, Washington, D. C., one went to Meharry Medical College, Nashville, and another to Atlanta University. The six grants will provide training for approximately 110 students for the next four years.

CANCER CENTER--The National Cancer Institute announced the award of a $1.2 million one-year grant to establish a specialized cancer center at the Mount Sinai School of Medicine of the City University of New York. The award partially supports salaries, equipment, supplies, alterations, and renovations at the Center. It also provides partial core support for an integrated research program including chemotherapy, immunotherapy, biochemical diagnosis, and supportive patient care. NCI will provide two additional years of comparable funding for this new center. More than 60 biomedical institutions across the country have specialized cancer centers supported by NCI. The centers conduct multidisciplinary cancer research, demonstrate research findings, and develop outreach programs with other hospitals and physicians in their areas.

News Releases Issued (Cont'd)

DEMONSTRATION CENTERS--The National Heart and Lung Institute (NHLI) will award more than $2,500,000 for the establishment of a National Research and Demonstration Center at the Baylor College of Medicine, Houston, Texas. The principal investigator is Dr. Michael E. DeBakey, chairman of the Department of Surgery and president of the College of Medicine. NHLI will also award more than $500,000 for the establishment of a similar Center at the King County Central Blood Bank, Seattle, Washington, The principal investigator is Dr. Dennis M. Donohue, director of the Blood Bank. These are two of the National Research and Demonstration Centers to be established early in fiscal 1975 under a provision of the National Heart, Blood Vessel, Lung, and Blood Act of 1972. The Act authorizes the eventual establishment and support of up to 30 such centers. The program of the Baylor Center will focus on heart and blood vessel diseases, particularly arteriosclerosis and its complications which, collectively, constitute the Nation's leading health problem. The program of the King County Central Blood Bank will be concerned with developing optimal procedures for the acquisition, processing, storage, distribution, and clinical use of blood and blood products.

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U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014

August 25, 1974

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Research Advances

IMPROVED TEST DETECTS INSECT STING ALLERGY

Each year, a significant number of people in this country die as a result of being stung by bees, yellow jackets, wasps, or hornets. It is estimated that as many as four in 1,000 persons stung by one of these insects have serious systemic reactions and, subsequently, live in fear of another sting.

Although the clinical symptoms of these reactions resemble anaphylaxis (a severe allergic reaction), it has not been possible to differentiate the allergic individual from the non-allergic by skin testing with extracts of insect bodies.

Now, using pure insect venoms, scientists at two of the National Institute of Allergy and Infectious Diseases' Asthma and Allergic Disease Centers have developed a laboratory test which clearly distinguishes sensitive patients from normal individuals. This research has also shown that most systemic (whole-body) reactions to insect stings are allergic in nature and not toxic, thus settling a long-disputed question.

In further studies, these investigators at Johns Hopkins University, Baltimore, and the State University of New York, Buffalo, have identified the major allergen of honeybee venom and suggest that it should be used diagnostically and therapeutically.

Anne K. Sobotka, Martin D. Valentine, M.D., Allen W. Benton, and Lawrence M. Lichtenstein, M.D., Ph.D., at Johns Hopkins, obtained leukocytes from 16 patients who had experienced symptoms suggestive of systemic

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anaphylaxis following an insect sting, and from 12 hospital employees with no history of insect allergy.

When the leukocytes of the 16 patients were challenged *in vitro* with several pure venoms, all but three samples released histamine, a chemical intimately involved in the allergic response. No normal individual had leukocytes which released histamine. Two of the three patients whose leukocytes failed to release histamine had been stung by unidentified insects whose venoms might not have been represented in the panel available for testing.

The patterns of the patients' reactions to the various venoms showed only limited cross-reactivity between these substances. Seven patients reacted only to the yellow jacket/hornet family of venoms; three only to honeybee venom; and three to both classes. This observation puts into question the common practice of skin testing and treating patients with a mixture of extracts prepared from the several insect families.

Of more fundamental importance is the question of use of whole-body insect extracts for skin testing and immunotherapy. In most instances, patients whose leukocytes readily released histamine in reaction to the purified venoms failed to respond to the whole-body extracts.

Further research results by Ms. Sobotka and her co-workers, and by Dr. C.C. Charvejasrn, John I. Wypych, Ph.D., Robert E. Reismin, M.D., and Carl E. Arbesman, M.D., of Buffalo, were reported at the annual meeting of the American Academy of Allergy in January. At that time these scientists reported that bee venom contains a specific antigen not present in significant amounts in whole-body extracts and that a substance called phospho-

(more)

lipase A is a major antigenic component of the venom.

In addition, the Johns Hopkins investigators noted that sera from two allergic patients who had been carefully treated with purified bee venom contained antibodies which could block the *in vitro* allergic response of sensitized leukocytes. The scientists agree that such immunization with honeybee venom deserves a carefully monitored early trial in appropriate patients.

Ms. Sobotka's report of venom-induced histamine release appeared in the March 1974 issue of the *Journal of Allergy and Clinical Immunology*.

#

KIDNEY FAILURE--Although methods are now being developed to save and extend the lives of many people with end-stage kidney disease, about 60,000 in the United States die each year because of irreversible kidney failure. This failure results from the common final stage of chronic kidney disease and urologic disorders, according to the National Institutes of Health.

Research Advances

ORAL PATHOLOGISTS COMPARE THREE CONFUSING LESIONS

A group of abnormal spots or lesions in the mouth, especially on the tongue, has been described and compared by a team of oral pathologists.

The scientists report that psoriasis, Reiter's syndrome, and varieties of geographic tongue may all be so similar clinically and histologically that diagnosis is difficult. The cause or causes of these psoriasis-like diseases is unknown; it is not even certain whether they are separate entities or different aspects or stages of one disease family, since cases have been reported in which one condition has progressed into another.

The scientists prefer the term "erythema circinata" to that of geographic tongue chiefly because the former describes the appearance of the lesions when they occur elsewhere than on the tongue. Then, if these flat, red spots with their scalloped, slightly raised, yellowish-white margins gradually creep to other parts of the mouth, they can be called erythema circinata migrans instead of the current, misleading term--ectopic geographic tongue.

This common type of lesion found in children and adults usually causes no discomfort, but occasionally there is a burning sensation. The migrans variety is quite rare, and may occur only once or intermittently for years.

Psoriasis is generally considered to be a chronic skin disease in which both psychosomatic stress and genetics may play a part. It is sometimes associated with non-rheumatoid arthritis. However, its lesions may appear intermittently on mucous membrane anywhere and are not limited, as is

(more)

commonly believed, to chronically scaling skin mostly on the hands, feet, and scalp. In cases documented as oral psoriasis by histologic studies, the lesions may be either raised, white, scaling patches, or flat, reddish areas with scalloped white borders very similar to those of erythema circinata.

Reiter's syndrome is most common in young males, and is usually associated with simultaneous occurrence of arthritis, conjunctivitis, and urethritis. The patients also may have scaling palms and soles. Quite often there is an association with gonorrheal organisms, but antibiotics do not cure the syndrome even after the bacteria have been vanquished.

The lesions in the mouth may begin as small, red or gray raised lumps or papules which later ulcerate, or, much like erythema circinata, they may appear as flat, reddish, scalloped patches. Histologically the mouth lesions resemble those of psoriasis.

At present, the scientists cannot tell whether erythema circinata (geographic tongue) is a relatively mild form of Reiter's syndrome, of psoriasis, or both; or whether three totally different conditions attributable to different causes happen to have a similar clinical appearance. They hope that others will add careful studies to theirs so that, in time, the causes can be unearthed and treatment improved for these puzzling conditions.

The research was reported by Dwight R. Weathers, D.D.S., of Emory University, Atlanta, Georgia; Gary Baker, D.D.S., of St. Joseph, Missouri; Howell O. Archard, D.D.S., of the National Institute of Dental Research; and E. Jefferson Burkes, Jr., D.D.S., of the University of North Carolina, Chapel Hill, in *Oral Medicine, Oral Surgery, Oral Pathology*, June, 1974.

#

Research Advances

DENTAL SCIENTISTS DISCOVER THIRD TYPE OF COLLAGEN

Dental scientists are discovering that unlike most protein molecules which are identical wherever they appear in the body, collagen, the chief protein of connective tissue, has at least three variants which are specific for certain tissues.

Scientists at the National Institute of Dental Research (NIDR) who have been studying collagen for several years explain that all collagen molecules are composed of three long chains coiled together for most of their length. Because chemical bonds cross-link the chains to each other, the molecule is quite stable. With age, collagen molecules also tend to cross-link and form thread-like bundles or fibrils which give skin, bone, cartilage, and other tissues much of their strength and toughness.

The first collagen studied came from skin or bones of young animals and was fairly soluble in salt solutions. Its chains were named alpha one and alpha two. The amino acid composition of the alpha one and alpha two chains has proved to be very uniform in all the animals that have been studied. In fact, several amino acid sequences follow an identical pattern, and the other segments or peptides of these chains are so similar that chemists can tell which are equivalent in various species.

This type of collagen molecule consists of a single alpha two chain coiled together with two alpha one (I) chains. This is the best known type and is found widely distributed in most tissues (skin, bone, teeth, tendon, arteries, uterus, fibro-cartilage).

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Collagen (Cont'd)

Collagen of another type was discovered a few years ago by Edward Miller, Ph.D., in Dr. Karl Piez's Laboratory of Biochemistry of NIDR. This molecule appears only in hyaline cartilage, and is the sole collagen in that tissue. It consists of three identical chains which are clearly distinct from alpha one (I) and alpha two chains, and is designated alpha one (II).

This finding excites scientists because they believe that a specific gene controls each protein, and that it is unusual to have multiple genes for synthesis of a structural protein, as the case appears to be now. Also it is always interesting that one of these genes, which are carried on chromosomes in every cell, should be expressed only in the cells of one specific tissue such as cartilage.

Now, Dr. Miller (presently at the Institute of Dental Research at the University of Alabama, Birmingham) reports the discovery of a third type of collagen. It is widespread in the body, but never appears in hyaline cartilage nor in calcified tissue such as bone and teeth. In this type of collagen, three alpha one (III) chains are coiled together.

Considerable chemical detective work has been necessary to study the third type of collagen because it is found chiefly in the insoluble residual material after the salt-soluble portion has been extracted. Dr. Miller's team uses pepsin to digest this material before attempting, via chromatography, to separate various chains and peptides split off by cyanogen bromide. Some general characteristics now begin to emerge.

The new chain has more glycine and hydroxyproline and less proline than other collagens. However, its chief difference lies in the presence

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of the sulfur-containing amino acid, cysteine. No other, mature, extracellular collagen contains cysteine, although it appears in procollagen within cells. Because the sulfur in cysteine forms disulfide bonds, the peptide at the carboxy-terminal end of the molecule, where the cysteine is located, is hard to separate. That portion usually chromatographs not as short, light, individual peptides, but linked to its similar neighbors in confusing double or triple units. This is why it took Dr. Miller's group some time to be sure that animal collagenase, an enzyme which splits other collagens into two segments one fourth and three fourths the length of the original molecule, was splitting type three the same way.

The investigators thought at first that sulfur bonding would make the new collagen very stable. However, further tests showed that the alpha one (II) chain of cartilage collagen is 100 times slower to cleave than the more familiar alpha one (I), and the new alpha one (III) chain is the fastest of all to cleave. Therefore, they guess that the new protein may turn out to be the most renewable form of collagen.

The scientists hope to learn more about the roles of the three types of collagen in various connective tissue diseases now that it is possible to distinguish them from each other and to identify them with the help of immune sera.

Much of the recent research on the new collagen has appeared in the March 22, 1974, issue of *Science* and further reports will appear in *Biochemistry* this summer.

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Photo Feature

LIBRARY EXHIBIT DEPICTS MEDICINE OF WORLD WAR I

The "War to End All Wars" posed a number of challenges to medicine. In an exhibit of historical materials, the National Library of Medicine (NLM) examines in detail the fascinating medical aspects of this conflict.

The exhibit, composed of photos, posters, books, and manuscripts from the Library's extensive collection of historical materials, focuses on the state of military medicine in World War I, its defeats, and its triumphs. Artifacts such as surgical kits and pathological specimens, on loan from the Museum of the Armed Forces Institute of Pathology, are also on display.

Medicine had made many important advances since the Civil War, and a real effort was made to incorporate this knowledge into the care of the war wounded during World War I. In spite of these innovations, the toll from battlefield wounds and disease was frightful and required the same heroic output of mind and endurance that all previous wars had demanded.

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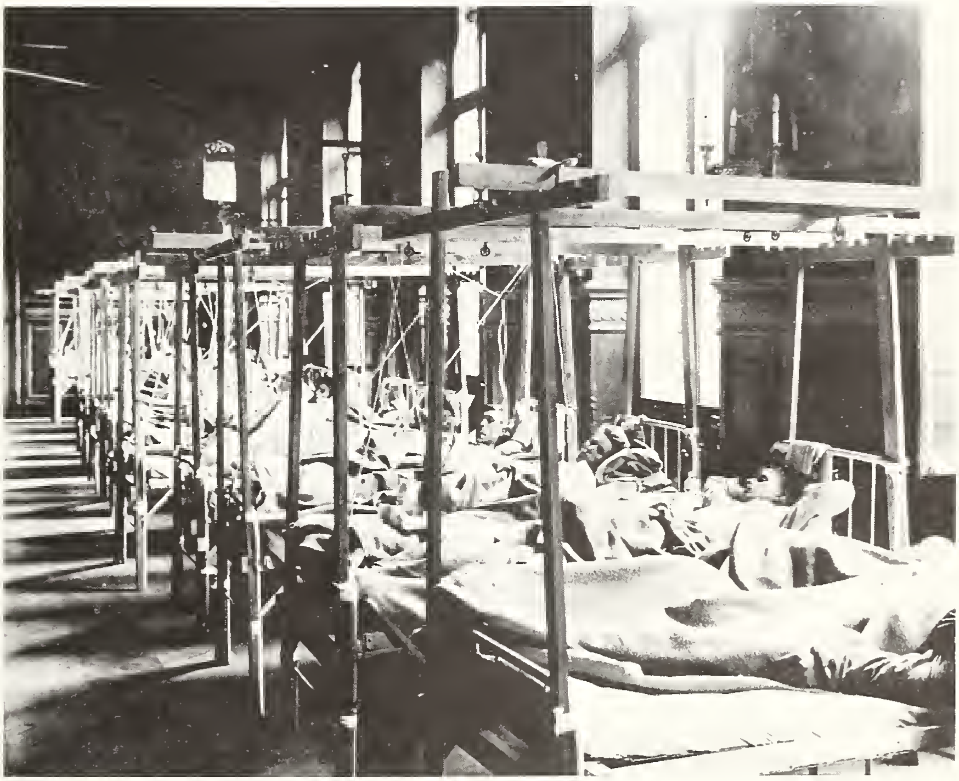
Part of the newly-motorized World War I ambulance corps is shown at Camp Hospital Number 11, St. Nazaire, France. (NIH Photo #1281)

Exhibit (Cont'd)

The NLM display delineates various medical aspects of the war, such as the tragic influenza epidemic which claimed millions of civilian and military victims throughout the world. The exhibit also details the effects of phosgene and mustard gas during battle, the operation of a newly motorized ambulance corps, and battlefield and sanitation methods.

The exhibit can be seen at the Library from 8:30 a.m. to 9 p.m. weekdays and until 5 p.m. on Saturdays, from September 2 to January 17.



Soldiers recuperate in a fracture ward of Base Hospital Number 1, Vichy, France. (NIH Photo #1282)

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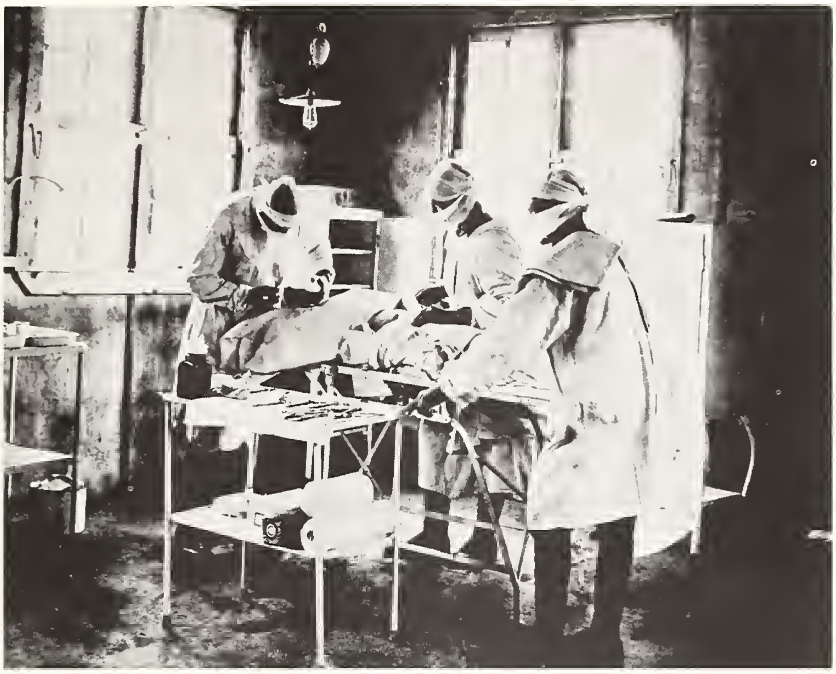
Exhibit (Cont'd)



This photo (above) of an operating room at Camp Hospital Number 5, Genicort, France, shows battlefield surgery techniques and sanitation methods. (NIH Photo #1283) Near Nantillois, France (left), soldiers "hunt for cooties" in an attempt to maintain some standards of good hygiene during the conflict. (NIH Photo #1284)

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Photo Feature

EXPANDING UPPER JAW IMPROVES BREATHING

Orthodontists at the University of North Carolina, Chapel Hill, have shown that widening the hard palate to improve occlusion also makes breathing through the nose much easier.

Bruce L. Stewart, D.M.D., H. Garland Hershey, D.D.S., and Donald W. Warren, D.D.S., Ph.D., report an increased ease of breathing for seven of their 15 patients. Since chronic mouth breathing prevents optimal warming, moistening, and filtering of air before it enters the lungs, mouth breathers may be subject to increased respiratory problems. Therefore, it is possible that expansion of the upper jaw to improve dental occlusion also improves the general health of these children.

According to the investigators, when the upper arch is too narrow, orthodontists can expand it with an appliance fixed to the upper teeth by bands. Pressure applied by a screw separates the two halves of the hard palate where they join along the median suture. The process is gradual so that new bone fills in the space while the dental arch of the upper jawbone expands enough, perhaps 10 millimeters, to fit over the lower teeth.

The beneficial effects of this procedure on occlusion and appearance are obvious, but secondary effects on the function of breathing are not.

Now, the Chapel Hill investigators report that expansion of the upper jaw greatly helped their patients' breathing. Many had experienced difficulty breathing through the nose in the normal way. Nasal resistance to the passage of air dropped and the flow of air increased markedly in all subjects. Also,

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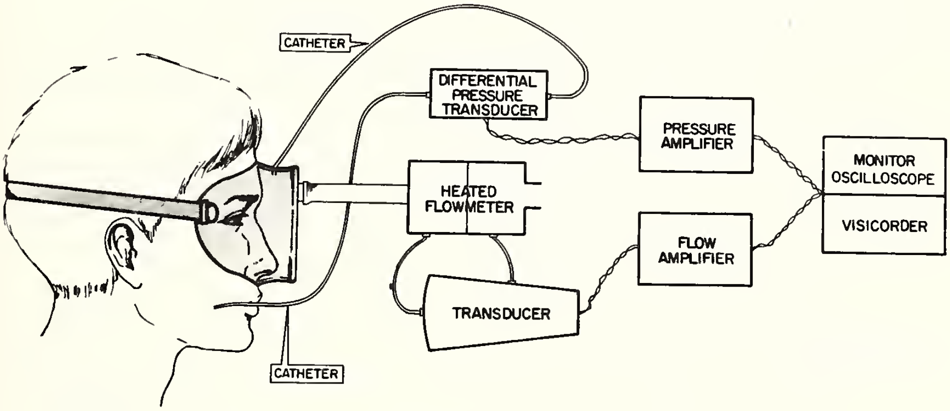
measurements made before and after expansion proved that air turbulence decreased. The changes were recorded by a pneumotachograph and a pressure transducer.

The work was supported by the National Institute of Dental Research.



A schematic diagram shows the equipment used by Dr. Stewart and his associates to measure breathing in orthodontic patients. (NIH Photo #1285)

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Photo Feature

For Echo-Cardiography...

ULTRASOUND TECHNIQUE MADE TWO-DIMENSIONAL

NIH scientists have developed a new imaging system that permits visualization of a large part of a beating heart.

Called two-dimensional echo-cardiography, this technique is particularly useful in examining infants and children for congenital heart disease. Previously ultrasound systems were only one-dimensional.

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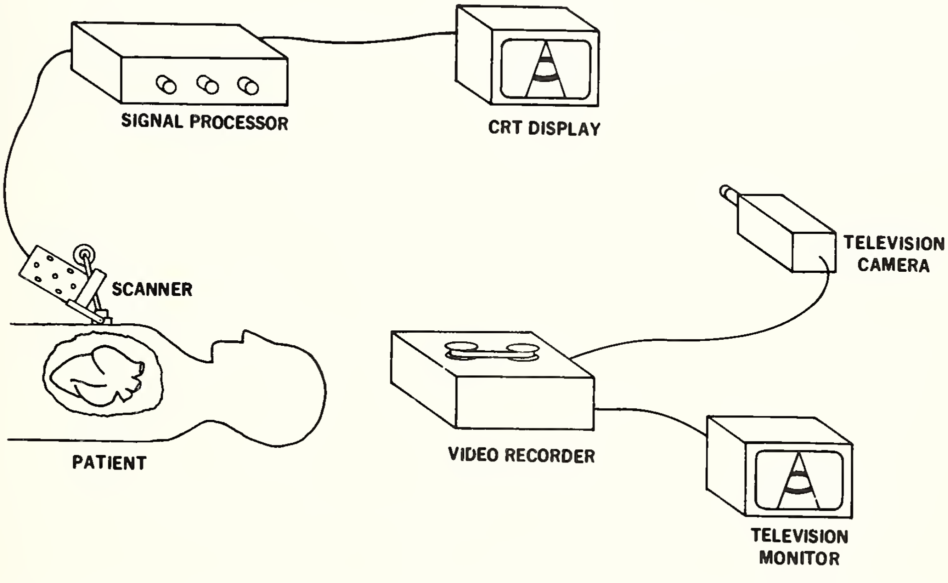

The diagram shows the NIH two-dimensional echo-cardiography system in use. The scanner, placed on the patient's chest, contains an electro-acoustical element which vibrates through a 30 degree arc. A television camera records the image on video tape. The image is subsequently viewed on a television monitor for diagnosis. (NIH Photo #1286)

Echo-Cardiography (Cont'd)

Because of the small size of the heart and blood vessels of children, this technique is expected to be particularly useful when a youngster requires a detailed heart examination or cardiac catheterization procedure.

The new scanning technique was developed by scientists at the National Heart and Lung Institute and the Division of Research Services. It produces 30 separate pictures of the heart per second, with each individual picture consisting of 100 lines-of-scan for detailed analysis.

The system, which is motor-driven, is relatively inexpensive. Many of the 3,000 U.S. medical centers that already have ultrasound units could adapt them for two-dimensional echo-cardiography.

The technique was described by James M. Griffith and Walter L. Henry, M.D., in *Circulation*, June 1974.

#

TRIGLYCERIDES--Triglycerides are neutral fat esters and the predominant lipid of adipose tissue as well as the predominant dietary lipid. The average American diet provides about a gram of triglyceride per pound of body weight daily, according to the National Institutes of Health.

Medical News Tip

APNEA ALARM SYSTEM--University of Washington scientists are developing an inconspicuous ultrasonic alarm system to monitor an infant's breathing.

Although the system is not connected to the patient, it can detect the respiration rate of an infant who is in an enclosed chamber or open crib. If the infant's respiratory rate falls below a minimally-acceptable level or if periods of apnea exceed a preset standard (usually 20 seconds), a light flashes and an alarm sounds. Such periods of apnea have been implicated in Sudden Infant Death Syndrome.

H. Fred Stegall, Ph.D., who is developing the system at the School's Center for Bioengineering, explains that the ultrasound is generated by a small transducer fitted into the Isolette cover, flooding the inside of the chamber with sound. Sound returning to the transducer remains constant in amplitude unless something moves inside the chamber. When the infant breathes, the amplitude fluctuates and is detected.

The research is supported by the National Institute of General Medical Sciences (NIGMS).

For additional details, contact:

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#

News Releases Issued

VENEREAL DISEASE--The Harvard School of Public Health is the recipient of a $152,057 program-project grant for venereal disease research. The grant, from the National Institute of Allergy and Infectious Diseases (NIAID), will support the first year of a Center for the Study of Sexually-Transmitted Diseases. The program will compare the epidemiologic importance of ten infectious microorganisms in genital infections. The agents to be pursued include the gonococcus and other bacteria, cytomegalovirus, chlamydia, herpes simplex virus, mycoplasmas, *Trichomonas vaginalis,* and certain fungi. (Chlamydia and mycoplasmas are microorganisms, some of which infect man, which are different from bacteria, viruses, fungi, or protozoa.)

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NEWS&FEATURES FROM NIH

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE ■ Public Health Service ■ National Institutes of Health ■ Office of Information ■ Bethesda, Maryland 20014

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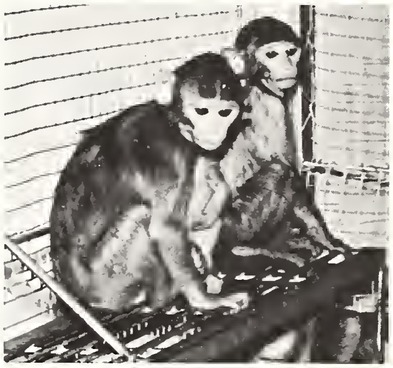

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Research Advances

CHEMICAL INDUCER OF INTERFERON PROTECTS AGAINST COLD SYMPTOMS

A drug known as propanediamine markedly reduces cold symptoms and virus shedding if administered prior to and immediately after exposure to cold-causing virus.

In a carefully controlled study of 39 young adults, National Institute of Allergy and Infectious Diseases grantees Charoen Panusarn, M.D., Edith D. Stanley, M.D., George Gee Jackson, M.D., Victor Dirda, and Mary Rubenis of the University of Illinois College of Medicine, Chicago, found that the effectiveness of propanediamine nose drops could be linked to the drug's ability to induce high levels of interferon.

Interferon is a substance produced naturally in the body in response to viral and some other infections. Since interferon, unlike antibodies, is not virus-specific, its use has been considered potentially promising in control of respiratory infections like the common cold which are caused by viruses too numerous to be assembled in one vaccine.

In natural infection with a respiratory virus, virus shedding precedes symptoms and peak illness by about 24-48 hours while natural induction of levels of interferon, which can stop extension of viral infection and relieve symptoms, requires 48 to 72 hours. Clinical investigation of common cold and other respiratory infections has been directed at changing the sequence of these natural events by applying medications, such as exogenous interferon, to suppress the virus or accelerate the natural response and repair.

In the University of Illinois study, the investigators randomly divided the volunteers into four groups: 15 subjects received propanediamine and

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rhinovirus Type 21; 14 were given a placebo prior to virus challenge which looked exactly like the milky, slightly viscous drug; five received propanediamine and an inert preparation (a "fake virus"); while five received both the placebo and the "fake virus."

Nose drops of the drug or the placebo were given three times on the day before challenge with the virus or the noninfectious preparation and twice the next day, four and eight hours after challenge. Each morning for 10 days the investigators took nasal specimens in order to determine the amount of virus shed and the level of interferon induced. They took blood samples on the day before and eight and 28 days after challenge to measure the amount of neutralizing antibody present. Eleven common cold symptoms such as sneezing, nasal discharge, and sore throat were monitored daily.

All persons receiving propanediamine developed high titers of interferon. Among antibody-free persons, drug treatment, as compared to placebo, decreased infectivity of the virus, markedly reduced symptoms of illness, and decreased virus shedding if infection occurred. Among persons with prechallenge antibody, drug treatment further increased resistance to infection, decreased the amount of virus produced, and prevented symptoms.

The investigators, in discussing their results, pointed out that the rapid appearance of interferon in nasal secretions after virus challenge of persons with preexisting antibody was completely unexpected. Although the mechanism of this phenomenon is not known, the scientists believe that it may suggest a more intimate role than has been previously demonstrated for cell-mediated immunity in host resistance to common viral respiratory infections.

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The investigators published a complete report of their results in *The New England Journal of Medicine*, July 11, 1974.

#

RENAL DISEASE--Renal diseases may drastically alter vital kidney functions; when the disease is chronic and progressive, symptoms may ultimately converge into a final common pattern of end-stage disease with irreversible kidney failure and its characteristic symptom uremia, according to the National Institutes of Health.

CANCER TREATMENT--Cancer treatment research has a three-pronged strategy according to the National Institutes of Health: understanding cancer at the molecular level, developing new anticancer drugs, and improving the quality of total therapy.

DIABETES--A complicated disease for which there is no known cure, diabetes ranks seventh on the list of diseases causing death in the United States, according to the National Institutes of Health.

Research Advances

DENTAL SCIENTISTS STUDY MECHANISM OF BONE LOSS

Scientists studying periodontal disease are finding new evidence relating the inflammation of soft tissue to the loss of hard tissue. A better understanding of these processes is needed to control and ultimately prevent the disease which robs millions of Americans of their teeth.

A major insight derived from recent research is that periodontal inflammation appears to be linked to immune reactions which occur when people become sensitized to products of particular bacteria. These suspect organisms are held close against the gums for long intervals in a film of dental plaque which collects at the base of teeth. Some of these immune reactions are directed by sensitized tissue cells; others depend on cells and complement in the blood stream.

Complement, a family of serum proteins that act in series, can be activated by antibody-antigen complexes. Such complexes form when a foreign substance--the antigen--gets into the body and is chemically bound to, or surrounded by, one or more antibody molecules (large globular proteins). Some complexes circulate in the blood, and others form on surfaces of cells.

After complement is activated, it can take part in a number of immune reactions such as neutralizing viruses, destroying certain cells, summoning scavenger cells to remove bacteria and foreign particles, directing the migration of particular cells in the blood stream to specific sites in tissue, increasing the permeability of blood vessels so that substances can enter and leave more readily, and triggering the release of histamine. All immune reactions do not involve complement, but it is essential to a great many.

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Another significant piece of periodontal evidence emerged recently when grantees of the National Institute of Dental Research (NIDR) showed that prostaglandin E (PGE) occurs at high levels in inflamed human periodontal tissues and that, in tissue culture, PGE can cause bone to disappear or resorb. The prostaglandins, a family of small, biologically active molecules derived from fatty acids, are made in many tissues and have diverse effects on the respiratory, circulatory, and reproductive systems.

A very recent development in the search for a relationship between immunologic reactions and bone loss is a collaborative study by five scientists who report that activation of complement at the surfaces of certain cells can trigger the synthesis of PGE, which then destroys bone.

The investigators cultured fetal rat bones labeled with radioactive calcium in a medium to which they added normal rabbit serum which contains complement. After three days, they found considerable PGE in the culture medium. The researchers detected early bone loss by the increase of radioactive calcium in the medium. After six days of culture, this increase was about 60 percent, and histologic changes were also visible under the microscope.

The lapse of time between the addition of complement and the increase of radioactive calcium suggested that a compound other than complement had to be involved in bone loss, and the previous research made PGE a likely candidate.

Bone resorption increased when the scientists added antibodies against bone (or a constituent of bone cells) that are specific for antigens present on cell surfaces. In their system, complement was activated by the interaction of these antibodies with cellular antigens. So it seemed to the investigators

(more)

that, in life, complement could also be activated in the same way by antibodies combined with bacterial products that might be attached to cell surfaces. Once activated, complement would trigger the manufacture of PGE which, in turn, damages bone.

The researchers showed that complement is necessary for the type of bone loss in their system. When they cultured rat bones with complement which had been inactivated by heat or which lacked one component, they found no increase in PGE or in bone loss. They believe that PGE mediates this bone loss because they found that indomethacin, a drug which inhibits the formation of PGE, blocked bone resorption even when they added active complement to their cultures.

This type of bone loss differs from that caused by hormone imbalance and may be important in some types of arthritis and other bone and connective tissue diseases.

Lawrence G. Rais, M.D., and Hollis A. Simmons of the University of Rochester; Ann L. Sandberg, Ph.D., and Stephan E. Mergenhagen, Ph.D., of NIDR; and Jo Max Goodson, D.D.S., Ph.D., of the University of California, San Francisco, published a report of their findings in *Science*, August 30, 1974.

#

Research Advances

Chemotherapy...

MARROW FROM IDENTICAL TWIN ENHANCES LEUKEMIA TREATMENT

A bone marrow transplant from a normal identical twin, in combination with chemotherapy, total-body irradiation, and immunotherapy, appears to provide a leukemia patient with a chance for a normal, active life.

NIH-supported scientists at the University of Washington, Seattle, used this combination to induce complete remission from several forms of leukemia in patients who no longer responded to conventional forms of treatment. The success of this combination of therapies suggests that its use should not be restricted to leukemia patients in the terminal stage of their illness. The treatment can be extended to any patient with a normal identical twin.

An identical twin is the perfect choice for a donor since the HL-A antigens (genetic markers) on the cells of the transplanted material and the recipient are the same. A mismatch of these genetic markers, which can be determined by several techniques, can result in a fatal development, graft-versus-host disease, in which the graft rejects and destroys the recipient.

Transplants of bone marrow (the blood-forming tissue which contains all the circulating blood cells and their precursors) are performed in the hope that the donor's immunologically competent cells will recognize and eliminate the foreign malignant cells in the recipient. To reduce the number of leukemic cells which these donor cells have to destroy, anti-leukemic drugs and supra-lethal doses of total-body irradiation are administered prior to the transplant.

(more)

The Seattle group transplanted 16 patients following chemotherapy and irradiation. After transplants, 12 patients additionally received immunotherapy consisting of transfer of large numbers of lymphocytes (the white cells most important in recognition of foreign substances or antigens) from their normal twins. This treatment was followed by weekly injections of the patient's own killed leukemic cells which provided a continuing stimulus to the infused lymphocytes so they could continue to eradicate any remaining live leukemic cells.

Eight of the 14 patients who achieved complete remission now (two-44 months later) lead normal lives without the need for any anti-leukemic drugs. An impressive feature of this study was that, unless leukemia recurred, the patients in remission were not susceptible to the frequently fatal infections which afflict recipients of grafts from non-twin donors.

Many current candidates for bone marrow transplants are frequently not in the strongest condition to tolerate the risks and toxic side effects of these methods of treatment--radiation, chemotherapy, transplantation, and immunotherapy. The researchers feel that if a patient could receive this combination of therapies as soon as his disease is diagnosed or when he is in his first remission induced by conventional therapy, the chances for success would be significantly enhanced.

Alexander Fefer, M.D., Albert B. Einstein, M.D., E. Donnall Thomas, M.D., C. Dean Buckner, M.D., Reginald A. Clift, F.I.M.L.T., Harold Glucksberg, M.D., Paul E. Neiman, M.D., and Rainier Storb, M.D., reported their findings in the June 20, 1974 issue of *The New England Journal of Medicine*. Dr. E. Donnall

(more)

Thomas is a recipient of a research career award of the National Institute of Allergy and Infectious Diseases. He is also supported by the National Cancer Institute and by NIH's Division of Research Resources.

#

KIDNEYS--The kidneys receive about one-quarter to one-fifth of the blood volume pumped by the heart, according to the National Institutes of Health.

ZPG--Zero Population Growth is reached when a population neither increases nor declines over a period of time--that is when the number of births and immigrants is balanced by the number of deaths and emigrants, according to the National Institutes of Health.

TRANSPLANT PATIENTS--Kidney transplant patients have few periodontal problems because drugs which suppress their immune responses also suppress inflammation in their mouths, according to the National Institutes of Health.

Photo Feature

In Detroit...

NEW MOBILE UNIT OFFERS SICKLE CELL SCREENING

The Comprehensive Sickle Cell Center at Wayne State University operates a unique "Sickle Mobile" to make screening available at many Detroit locations.

"Because only a limited number of people can conveniently reach our permanent office," explained Charles F. Whitten, M.D., Center Director, "we are taking our trailer to carefully-selected other sections of the city."

The "Sickle Mobile" is outfitted to perform many free services quickly and efficiently. Staff members draw and test blood, show an educational film, discuss blood test results, and--if appropriate--provide a counseling session.

Wayne State University has one of the 15 Comprehensive Sickle Cell Centers supported by the National Heart and Lung Institute. Rudolph Jackson, M.D., is coordinator of the National Sickle Cell Disease Program.

Detroit residents who visited the Michigan Employment Security Commission recently were offered a free sickle cell test in the "Sickle Mobile" parked outside. (NIH Photo #1287)

(more)

"Sickle Mobile" (Cont'd)

Drawn blood is tested immediately so that results and their significance can be discussed promptly. (NIH Photo #1288)

While waiting for blood test results (left photo), the men and women watch an educational film about sickle cell and the sickle cell program. Dr. Whitten (left) is often available to answer additional questions. (NIH Photo #1289)

When appropriate, private counseling sessions are offered in the "Sickle Mobile." (NIH Photo #1290)

#

News Feature

DRR TAKES STEPS TO ASSURE SUPPLY OF RHESUS MONKEYS

In anticipation of severe shortages in rhesus monkey supply in the next five years, the Animal Resources Branch of NIH's Division of Research Resources has initiated the NIH National Plan for Rhesus Monkey Supply which calls for the establishment of large breeding colonies in the United States to supply extramural researchers.

The Branch awarded domestic monkey-breeding contracts to Litton-Bionetics, Inc., and Hazleton Laboratories, Inc. in June.

Hazleton Laboratories, recipient of a first-year contract for $289,000, will establish a breeding colony near Edinburg, Texas, with anticipated annual production of 500 infant rhesus monkeys after the fourth and fifth years. Litton-Bionetics received an 11-month initial contract in the amount of $191,000 to provide a sufficient number of breeding animals to produce 400 infant rhesus monkeys annually after four or five years at Yemassee, South Carolina.

The Veterinary Resources Branch of NIH's Division of Research Services, has undertaken a similar breeding program to provide primates for NIH intramural researchers.

India, the main source of supply for rhesus monkeys, has indicated reduced exports of monkeys in the next several years. In past years, India was exporting 50,000 monkeys annually to the world; last year, this figure was cut to 30,000.

The 28,000 rhesus monkeys imported annually in this country represent about 50 percent of all nonhuman primates acquired for all biomedical

(more)

activities. Approximately 13,000 are used by the pharmaceutical industry for the development, production, and testing of pharmaceuticals and biologics; 9,000 by non-government medical research organizations; 3,000 by intramural NIH and the Food and Drug Administration's Bureau of Biologics; and 3,000 by other government agencies.

In June 1974, William J. Goodwin, Ph.D., director of NIH's Primate Research Centers Program, reported to the Zoological Society of London on the current state of primate breeding in the United States. According to Dr. Goodwin, the NIH Primate Research Centers are producing approximately 50 percent of their own requirements for rhesus monkeys. Dr. Goodwin explained several actions taken to increase the domestic supply of rhesus monkeys in future years.

The Caribbean Primate Research Center has had a colony of free-ranging rhesus monkeys for several years. Recently, the Bureau of Biologics contracted for the development of a free-ranging breeding colony of 1,000 rhesus monkeys on the off-shore Puerto Rican island of La Cueva. The Bureau of Biologics is also negotiating for another 1,000-monkey rhesus breeding colony with NIH's Delta Primate Research Center at Covington, Louisiana. It will require at least three years for these four colonies to reach full production of more than 2,500 infant rhesus monkeys annually.

At the Charles River Laboratories, an outdoor breeding colony of 700 rhesus monkeys has been established on an island in the Florida keys. This operation is partially supported by the Animal Resources Branch in order to investigate the commercial feasibility of producing rhesus monkeys under island conditions.

#

Photo Feature

COMPUTER-ULTRASOUND SYSTEM HELPS ONCOLOGIST PLAN RADIATION THERAPY

A new interactive computer ultrasound system enables the oncologist to arrive quickly and efficiently at a plan for radiation treatment. On-line computer graphics techniques and the application of ultrasound allow the oncologist to visualize dose distribution and tumor location, and to consider possible therapeutic alternatives.

In the procedure, at the therapy planning station in the Radiation Oncology Department, Loma Linda University Medical Center, the patient is fitted with a plastic case for immobilization in the anticipated treatment position. James M. Slater, M.D., (right), positions the scan unit on the patient's body to generate echograms of the desired body area which appear on the monitor. William T. Chu, Ph.D., (left), used a sonic pen to trace the tumor and pertinent anatomical structure in various colors on the graphics display.

The system interacts with the Loma Linda Scientific Computer Facility which is supported by NIH's Division of Research Resources. (NIH Photo #1291)

#

Medical News Tip

PRODUCTION OF ANTIBODIES--Recent findings may help explain how a normal human body can produce an almost infinite number of custom-fitted antibodies to protect against hundreds of thousands of bacteria, viruses, and other foreign agents.

Philip Leder, M.D., head of a research team at the National Institute of Child Health and Human Development, estimates that a human being requires a million or more antibodies, or immunoglobins, to achieve and maintain normal immune status. Chemical and biological evidence from animal specimens, he says, suggests that each antibody might be produced by a combination or fusion of several genes. As had been known for many years, antibodies are composed of two light and two heavy chains of protein. Part of each chain is a constant (C) region, common to all antibodies. Added to it are several variable (V) or custom-made regions, targeted specifically to an individual foreign agent.

The NIH scientists have now demonstrated that a single gene or gene sequence directs the production of the C region and is used again and again in antibody production. Only the genetic instructions that direct the manufacture of the antibody's V regions are distinctive and require individual gene segments.

For additional information, contact: Jane Collins, Bldg. 31, Room 2B-03, NIH, Bethesda, MD 20014, Phone: (301) 496-4143.

#

New Publication:
Smoking and General Mortality Among U.S. Veterans, 1954-1969

Stopping the cigarette habit appears to increase the prospects for survival, even if this is done relatively late in life and after many years of smoking.

This is one of the findings reported in *Smoking and General Mortality Among U.S. Veterans, 1954-1969*, a new publication from the National Heart and Lung Institute. The report describes mortality related to the use of tobacco among 293,958 U.S. veterans who held Government Life Insurance policies in 1953. Questionnaires on smoking habits were circulated to this group in 1954 and 1957.

According to the survey findings, persons who had never smoked had the lowest probability of death during the 16-year period of followup. Mortality levels were highest among cigarette smokers, followed by cigar and pipe smokers. In each category, mortality risk was related to the amount smoked. Among persons who stopped smoking cigarettes--for reasons other than doctor's orders--mortality risk was lower than that among persons who continued to smoke. It remained higher than the mortality risk of persons who had never smoked, but declined as the period of abstinence increased until, after prolonged abstinence, it was only slightly higher in some groups of ex-smokers than that of non-smokers.

Science writers can obtain a free copy of this publication from NHLI, Building 31, Room 5A-21, NIH, Bethesda, MD 20014, Phone: (301) 496-4236.

#

News Releases Issued

DEMONSTRATION CENTER--The National Heart and Lung Institute will award approximately $900,000 for the establishment of a National Research and Demonstration Center at the University of Vermont, Burlington. The principal investigator is Dr. Gareth M. Green, professor of Medicine at the University of Vermont College of Medicine. This is one of the Research and Demonstration Centers to be established early in fiscal 1975. The program at Vermont will concentrate on lung diseases, with special emphasis on occupational pulmonary disorders resulting from prolonged exposure to harmful dusts and fumes in various industries and occupations.

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Research Advances

Infant Diarrhea...

SCIENTISTS PRESENT FIRST REPORT OF VIRUS-LIKE AGENT IN THE U.S.

Diarrhea of infants and children in Australia, England, Canada, and the United States may have a common cause, according to scientists at the National Institute of Allergy and Infectious Diseases (NIAID) and Children's Hospital of the District of Columbia.

Albert Z. Kapikian, M.D., of NIAID and his co-workers have reported convincing evidence that a virus-like particle, previously observed in the stools of young patients with severe diarrhea in Melbourne (Australia), Birmingham (England), and Toronto (Canada), is the actual cause of the disease in Washington, D.C., children. This is the first report of the presence of this virus-like agent in the United States.

In addition, the NIAID-Children's Hospital scientists have developed the first practical laboratory test for the new agent, a complement fixation test. Development of this test should be of great importance in unraveling the natural history of so-called "infant diarrhea" in many parts of the world. Additionally, identification of the cause of this disease may lead eventually to development of a

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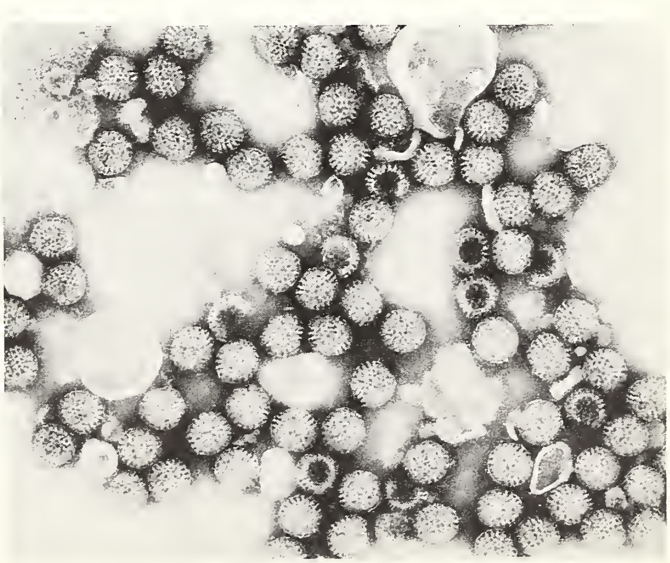

Reovirus-like particles observed in a stool filtrate made from a stool specimen from a young patient with acute gastroenteritis, are shown in the photo. These particles were observed following suitable preparation of the filtrate for examination by electron microscopy (magnification - 224,250). (NIH Photo #1292)

vaccine or other means of preventing this major health problem.

The U.S. investigators believe that it is possible that the new agent, first discovered by Australian scientists, will emerge as a major cause of non-bacterial and non-parasitic diarrhea of infants and children. Until the recent studies, the cause of most such diarrhea has not been known.

In their studies, the American investigators used immune electron microscopy (IEM) as well as conventional electron microscopy to detect virus-like particles in filtrates made from stool specimens of 13 of 21 youngsters hospitalized at Children's Hospital with gastroenteritis. The scientists also used IEM to test paired sera (one obtained during the acute stage of illness and another about three to six weeks later) for evidence of an increase in antibody to the virus-like agent. They found a significant rise in antibody specific for the agent in paired sera from selected patients whose stool specimens had contained the particles. Such an antibody response to a virus is considered laboratory evidence of infection.

When the scientists examined stool specimens from other patients hospitalized at Children's Hospital for respiratory disease or returning for well baby care, they found the virus-like particles in only one of 14 specimens. This was a filtrate from a stool of a two-month-old infant who developed diarrhea shortly before his admission with pneumonia.

In further studies, the NIAID and Children's Hospital investigators determined that the new virus-like particle was not related to agents causing community or institutional outbreaks of acute gastroenteritis. Also, it was not related to the three known reoviruses or 20 orbiviruses tested which the

(more)

agent resembles in size and shape. However, tests did show a relationship between the new particle and a virus which causes diarrhea in infant mice and another which causes diarrhea in newborn calves, viruses which the new agent resembles in size and shape.

Associated with Dr. Kapikian in these studies were Hyun Wha Kim, M.D., William J. Rodriguez, M.D., Sydney Ross, M.D., and Robert H. Parrott, M.D. of Children's Hospital and Richard G. Wyatt, M.D., W. Lee Cline, and Robert M. Chanock, M.D., of NIAID. They published their work in *Science*, September 20, 1974.

#

MENTAL RETARDATION--Neurological disorders caused by biological factors account for a large percentage of the mentally retarded. These factors include any which cause physical or chemical damage to the brain or nervous system, according to the National Institutes of Health.

LIFE SPAN--Since 1900, the average life span in this country has increased from 49 to 71 years, according to the National Institutes of Health.

Research Advances

SUBSTITUTIONS FOR TABLE SUGAR WILL NOT REDUCE TOOTH DECAY

Hope for reducing tooth decay by substituting other sugars for table sugar is dim, according to William H. Bowen, Ph.D., acting chief of the Caries Prevention and Research Branch of the National Institute of Dental Research.

Dr. Bowen recently described dietary experiments with monkeys performed in London while he was a fellow of the Royal College of Surgeons.

The old world monkey, *Macaca fascicularis (irus)*, is a good model for dental research, Dr. Bowen said, because it thrives on a human diet and harbors many of the same bacteria found in people. The animal is also important because its tissues react to dental diseases in ways that are histologically indistinguishable from those of human patients, and its teeth are large enough to accommodate ordinary instruments.

Tooth decay develops only when three factors interact and it is difficult to control even one of these disease factors in human research. However, animal experiments provide the clearest information about this extremely complicated disease, according to Dr. Bowen. He explains that germfree animals have no caries regardless of diet or genetic factors and that these animals, even when infected with bacteria taken from decayed human teeth, will not develop decay when their diet lacks fermentable carbohydrates. Also, an individual must have susceptible teeth for caries to occur. Some animals and humans have a greater resistance than others to the same challenges from bacteria and diet.

(more)

"It should be possible," Dr. Bowen said, "to break the caries chain at any one of these three links, and many people have suggested that table sugar is a vulnerable spot in the diet link." Without a bacterial mechanism for colonizing on teeth, saliva will either wash microorganisms away or dilute their acid byproducts below the danger point. Many kinds of bacteria are found enmeshed in a sticky film of plaque that covers teeth. This plaque not only enables organisms to attach to the smooth, vertical surfaces of teeth despite saliva, but also seems to prevent saliva from neutralizing or diluting accumulated bacterial acids. Since this ability of plaque is thought to be due primarily to small amounts of sticky, insoluble polysaccharides manufactured from sucrose chiefly by bacteria of the *Streptococcus mutans* group, it follows that removal of sucrose from the diet should decrease plaque and reduce tooth decay. Supporters of this argument note that a tremendous increase in tooth decay has coincided with the increased consumption of sugar throughout the world.

Dr. Bowen believes that this premise fails to consider some other important factors. First, the risk of decay for any person depends primarily on how often one eats sugar, not on how much is eaten per day or year. Swedish studies done 20 years ago proved this. The acidity of plaque rises rapidly each time sugar is eaten and stays high for about 20 minutes. A pH of 5.5 will dissolve enamel, and plaque pH has frequently been recorded as low as 4.2. Therefore, a person who customarily has only three meals a day, even if they are rich in sugar, is at less risk than another who consumes a smaller amount of sweets but nibbles them all day long.

(more)

The second group of factors--how bacteria interact under different dietary conditions--was explained by Dr. Bowen in the following experiments. First, he kept monkeys for three years on a decay-promoting diet containing sucrose and at the start of the experiments noted the proportions of various kinds of organisms in their plaque. Then each day he gave each animal a basic portion of its food by stomach tube throughout the 12-week experimental period. He also collected and analyzed the bacteria in the animals' plaque weekly.

For the first four weeks of the experiment, the animals received no food by mouth. During the second four weeks, Dr. Bowen divided the monkeys and fed one group a supplement of protein (casein) by mouth while the other group received invert sugar (glucose or fructose) in the same way five times a day. For the final four weeks, he reversed the diet of the two groups. At the end of the experiment, all animals were returned to their original cariogenic diet administered by mouth, and three months later they were again analyzed for plaque bacteria.

Dr. Bowen reports that changes in diet did affect the numbers and proportions of organisms in plaque and the ability to acidify, although plaque persisted regardless of diet. He found further that the organisms present in plaque when all food was tube fed, as well as when casein was the only food in the mouth, had very little ability to make acid even when the animals were given an experimental dose of sugar. Indeed, the numbers of streptococci, lactobacilli, and yeasts dropped drastically during tube feeding.

(more)

Feeding casein by mouth increased the formation of calculus, a mineralized deposit that surrounds the bases of teeth, the investigator explained. Also, the presence of either casein or an invert sugar allowed many more lactobacilli and yeast to grow in plaque than did tube feeding, although they did not reach their original profusion.

The numbers of streptococci, which decreased during casein consumption, increased rapidly again when invert sugars were available. In fact, three months after the monkeys resumed their original cariogenic diet, the streptococcal counts were higher than at the start of the experiment.

Therefore, because bacteria thrive and make abundant acids on the simple sugars as well as they do on sucrose, and because they develop plaque in the absence of sucrose, Dr. Bowen believes that replacing table sugar with other sugars will not reduce tooth decay significantly.

Dr. Bowen presented his findings at the meeting of the American Chemical Society, September 11, 1974, in Atlantic City, New Jersey.

#

COMMON COLD--Estimates of the annual incidence of the common cold indicate an average of eight colds per year for children under four years of age and two colds per year for adults for a total of as many as one billion colds per year, according to the National Institutes of Health.

Research Advances

In the Literature:
American Journal of Tropical Medicine and Hygiene, January 1974

DISEASE IN MONKEYS SHEDS LIGHT ON HUMAN KIDNEY DISEASE--Rhesus monkeys infected with the organism which causes the tropical disease trypanosomiasis develop a kidney condition similar to the serious human diseases known as glomerulonephritis.

According to investigators supported by the National Institute of Allergy and Infectious Diseases, experimental trypanosomiasis in the monkey may actually be a valuable model for studying the mechanisms of human kidney damage.

Glomerulonephritis, an inflammation of clusters of kidney blood vessels (known as the glomeruli), is thought to be an immunologic complication following a variety of infections. This theory is supported by such immunologic phenomena as a decrease in the level of serum complement that indicates its utilization in immune reactions, and the presence in the patient's glomeruli of deposits of antigen-antibody complexes.

Antigen-antibody complexes activate complement, a system of blood serum proteins in several ways. One way involves properdin, a serum component which reacts with antibody to kill viruses and bacteria. Properdin has been found in the glomeruli of patients with certain forms of glomerulonephritis.

In the present study, scientists at the Walter Reed Army Medical Center and the University of Connecticut found glomerular abnormalities in 15 out of 16 monkeys infected with *Trypanosoma rhodesiense,* an agent of trypanosomiasis. Of the four infected animals on which serologic studies were done, three had decreased serum complement levels and deposits of antibody, complement com-

(more)

ponents, and properdin in their glomeruli.

The investigators believe that this presence of properdin indicates that complement activation is similar in monkeys infected with trypanosomes and in glomerulonephritis patients.

They suggest that this experimental infection be considered a model for human glomerulonephritis and that since the properdin pathway may also be functioning in humans infected with African trypanosomiasis, a careful study of their renal function and structures should be made.

The investigators are: Ray B. Nagle, M.D., Herbert O. Lindsley, M.D., Elvio H. Sadun, D.Sc., Anthony J. Johnson, and Paul K. Hildebrandt of Walter Reed; and Peter A. Ward, M.D.,and Robert E. Berkaw of the University of Connecticut Health Center, Farmington.

#

RHINOVIRUS--Once a rhinovirus infects the body, a cold usually develops. The importance of other factors such as chilling, exposure, and overheating has not been demonstrated, according to the National Institutes of Health.

Photo Feature

Ready Soon...

DOCTORS TO SEE ALASKAN PATIENTS VIA SATELLITE

Even though only a few people will be seeing a new medical television program this Fall, the show will rate high in terms of bringing modern health care to remote Alaskan Indians.

Medical scientists in Tanana and Anchorage, Alaska will soon be "seeing" patients in the small, remote villages of Galena and Fort Yukon via NASA's Applications Technology Satellite (ATS-6).

Advanced testing of the ground-based transmission equipment is nearly completed for this mission of the ATS-6, which was launched on May 30 from the Kennedy Space Center. (See *NFFN* for June 10, 1974.)

The National Library of Medicine's Lister Hill National Center for Biomedical Communications is coordinating the ATS-6 medical services and educational programs. NLM is working with the Health Services Administration and the Health Resources Administration.

Alaskan Indians will report to community health stations to be "seen" by medical specialists at distant locations. (NIH Photo #1293)

(more)

Satellite (Cont'd)

The patient will be on the examination table (foreground) near the television camera (top left). A monitor (right) will be used by the community health worker to position the patient. (NIH Photo #1294)

Medical specialists will see the patients on the screen, and will be able to prescribe treatment and follow the patients' progress. (NIH Photo #1295)

The physicians will be able to see clear pictures of most body parts. Here an ophthalmologist is examining a patient's eye. The photos of the patients are scrambled so that no non-medical receiving station can see the patients. (NIH Photo #1296)

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Photo Feature

NEW TRAINING COURSE UPGRADES ANIMAL CARE

Sparked by the new "Laboratory Animal Care" Training Course, veterinarian Roy Hendrickson, D.V.M., (left) at the California Primate Research Center, shows James Batchelor (right) and Jerry Adams the proper technique for restraint of rhesus monkey during passage of a stomach tube. The new training series is intended to upgrade animal care technicians' skills and improve employee productivity in laboratory animal facilities throughout the country. The training series was developed by Joseph S. Spinelli, D.V.M., director of the Animal Care Facility of the University of California, San Francisco under a contract from NIH's Division of Research Resources. (NIH Photo #1297)

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Photo Feature

Workshop Planned...

NIGMS FUNDS ANESTHESIOLOGY RESEARCH AT FIVE CENTERS

The National Institute of General Medical Sciences (NIGMS) is supporting work at five Anesthesiology Research Centers in the United States. Scientists at the centers are studying anesthesia as a basis for improved surgical patient care, for respiratory assistance, and for relief from chronic pain.

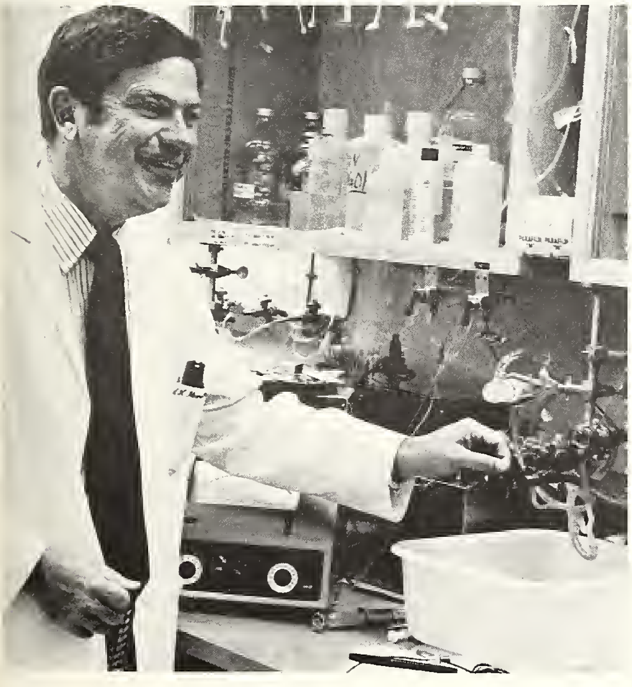
Locations of the centers are Columbia University, New York; Massachusetts General Hospital, Boston; University of California, San Francisco; University of Pennsylvania, Philadelphia; and University of Washington, Seattle. The principal investigators at these centers, along with dozens of other anesthesiology researchers, will participate in the NIGMS Anesthesiology Research Workshop at NIH on October 10 and 11. Scheduled discussions include anesthesiology research objectives involving respiration, cardiovascular system, central nervous system, metabolism, basic mechanisms, new anesthetic agents, pain, and acupuncture.

John J. Bonica, M.D. (left), is principal investigator of the NIGMS Anesthesiology Research Center at the University of Washington. Shih-hsun Ngai, M.D. (right), heads the NIGMS Anesthesiology Research Center at Columbia University. (NIH Photos #1298, 1299)

(more)

Anesthesiology (Cont'd)

Richard J. Kitz, M.D., is principal investigator of the NIGMS Anesthesiology Research Center at Massachusetts General Hospital. He is shown adjusting an automatic titrator used to measure the influence of anesthetics on enzyme activity. (NIH Photo #1300)



Two other principal investigators are William K. Hamilton, M.D. (left), at the University of California, San Francisco, and Harry Wollman, M.D. (right), at the University of Pennsylvania. (NIH Photos #1301, 1302)

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Medical News Tip

METIAMIDE: A POSSIBLE ANTI-ULCER DRUG--Metiamide, an antihistaminic drug recently developed in England, holds promise as a new anti-ulcer medication.

In animal studies, this agent proved capable of completely blocking histamine-induced gastric acid secretion. Preliminary human trials of metiamide in the U.S. now have verified the efficacy of single oral doses of the drug in sharply reducing excess gastric acid secretion without any apparent undesirable side affects. Studies revealed that the agent suppresses food-stimulated acid secretion below the level believed necessary to develop or to maintain a duodenal ulcer. Therefore, unless tolerance to the drug develops or toxic effects become evident, careful use of metiamide should hasten healing and prevent recurrence of duodenal ulcers in man. The cautious hope now exists that metiamide represents a truly physiological approach to ulcer control and one that may be the forerunner of many new anti-ulcer agents.

For information about current studies of metiamide, contact the National Institute of Arthritis, Metabolism, and Digestive Diseases, Bldg. 31, Room 9A-04, Bethesda, MD 20014, Phone (301) 496-3583.

#

New Publication:
The NINDS Parkinson's Disease Research Program

Parkinson's disease is a progressive neurological disorder affecting the brain centers responsible for control and regulation of movement.

Recent studies have shown that in Parkinson's disease there is a depletion of dopamine, one of the biogenic amine substances in the brain necessary for nerve transmission. Researchers have found that it is possible to replace the missing dopamine by a gradual buildup of large oral doses of L-Dopa, an amino acid. This treatment benefits about three-fourths of all parkinsonism patients. L-Dopa has been widely acclaimed as the first truly successful anti-parkinsonism drug, and its use has opened up new hope for patients.

The National Institutes of Health has had a long standing responsibility for research and research support in parkinsonism, dating from the establishment of the National Institute of Neurological Diseases and Stroke (NINDS) in 1950. The Institute's new publication, *The NINDS Parkinson's Disease Research Program*, discusses advances that have been made in treatment of the symptoms of Parkinson's disease. Gains made thus far, together with expected developments in the near future, have justified an optimistic attitude among researchers, physicians, and patients that control of this disabling disease can be achieved.

Science writers can obtain a free copy of this publication from:

NINDS
Building 31, Room 8A-03
Bethesda, MD 20014
Phone: (301) 496-5751

#

News Releases Issued

COMPUTER TECHNOLOGY--The National Library of Medicine will support training activities to promote the integration of computer technology into the teaching, practice, and research phases of clinical medicine. Under the program, authorized by the Medical Library Assistance Act, the Library will make a limited number of grants to support institutions in preparing health science professionals to apply computer techniques to health care information processing and health science education. Schools of medicine, osteopathy, dentistry, veterinary medicine, optometry, podiatry, and pharmacy qualified to conduct the proposed training activities are eligible to apply for the grants.

CANCER PROGRAM--The National Cancer Institute (NCI) announced the award of almost $10 million to 12 state health departments for a three-year program to screen low-income women for cancer of the uterine cervix. With this support, the health departments will make 1,194,000 screenings during the three years at an average cost of nine dollars per screening. About 306,800 screenings will be made the first year. Eight additional state health departments have one-year contracts to plan cervical cancer screening programs. NCI-funded screening programs are beginning in the following states: Connecticut, Kentucky, Louisiana, Michigan, Mississippi, Nebraska, New York, Ohio, Oklahoma, South Carolina, Tennessee, and Texas. One-year planning contracts have been awarded to: Arizona, California, Missouri, Nevada, Maine, Minnesota, Washington, and Wyoming.

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Research Advances

Brittle Hair, Short Stature...

INTELLECTUAL IMPAIRMENT FOUND IN AN AMISH GROUP

In a "closed population" such as the Amish of northern Indiana, genetic traits among families can be traced to common ancestors through three or four generations.

Charles E. Jackson, M.D., of the Henry Ford Hospital, Detroit, is compiling information on the relationship between inherited traits and physical abnormalities in this population before the young people in the group break away from their enclosed communities. Once the genes are assimilated into the general population, it will be harder to trace their origins and treat the consequences of these traits.

Dr. Jackson and associates Lester Weiss, M.D., and John H.L. Watson, Ph.D., found 25 individuals with a syndrome of brittle hair, short stature, and intellectual impairment in one large Amish kindred in Indiana. The number of affected individuals and their distribution provided evidence for the autosomal recessive inheritance of the condition and for the resultant decreased fertility.

The investigators observed that in 20 of these affected individuals the short stature and intellectual impairment were relatively mild. Although formal intelligence testing could not be obtained in this field study, the individuals were reported by their families as being slow learners who had done poorly in school, especially when compared with unaffected siblings. However, they appeared to function fairly well in their rural community.

(more)

The height of the affected individuals was one standard deviation or more below the mean for their age and sex and they were shorter in stature than their unaffected siblings.

The hair in each affected individual had an abnormal appearance on light, polarization, and scanning electron microscopy, and showed an irregular grooved surface lacking in scales. Surface changes similar to those in head hair were found in hair of the beard, eyebrows, eyelashes, axillary and pubic areas.

The investigators found no abnormalities when they studied the affected individuals for trace elements. However, the sulfur content in 11 affected individuals averaged 2.51 percent by weight, which is approximately one half that of controls.

Additionally, they noted that married affected individuals had very few offspring for a population known for its large families. An average of only 0.81 children per couple was born to all 11 affected married individuals as compared to 2.85 per couple for their 40 married unaffected siblings and 6.41 for their parents.

It is known that as hair is progressively formed, moving up the follicle, there is a maturation process which includes the gradual incorporation of cystine and the gradual accumulation of disulfide bonds. This developmental process is important to the structural stability of the hair. In the formation of sperm, there is also a maturation process in which disulfide linkages are established. Therefore, according to Dr. Jackson, the relative infertility

(more)

observed in this family may be due in part to a decrease in disulfide bonds in the sperm.

Each affected individual in the Indiana study is the result of a consanguineous mating and all can be traced to common ancestors who immigrated from Switzerland to the United States in 1763. If the gene for this condition was present in this couple, the condition can be expected to be prevalent in their many descendants, which numbered 9,016 in 1911. The mild retardation and slightly impaired growth could easily have been overlooked in many previous Amish studies.

The investigators published a report of their study in *Pediatrics*, August 1974. The work was supported by a grant from the National Institute of Arthritis, Metabolism, and Digestive Diseases.

#

EARLY STUDIES--The first scientific studies of Rocky Mountain spotted fever took place in Montana during 1902, according to the National Institutes of Health.

EARLY CANCER RESEARCH--The Public Health Service established a Special Cancer Investigations Laboratory at Harvard Medical School on August 1, 1922, according to the National Institutes of Health.

Research Advances

TECHNIQUE AIDS DIAGNOSIS OF MULTIPLE MYELOMA

An improved technique for early diagnosis of multiple myeloma, a malignant tumor of the bone marrow plasma cells, has been developed by two physicians at the University Hospitals of Cleveland.

George M. Bernier, M.D., and Richard C. Graham, Jr., M.D., have used electron microscopy to establish a method to allow physicians to differentiate more accurately between a non-malignant tumor of plasma cells and a malignant tumor. Dr. Bernier is director of Medical Oncology and Dr. Graham is head of the Division of Infectious Diseases at the hospital. Their analysis of bone marrow cells from 65 patients was supported in part by the NIH Division of Research Resources.

Multiple myeloma, which affects people age 50 and older, is basically a tumor of an antibody-producing cell, the plasma cell. The patient complains of neuralgic pains and later painful swellings appear on the ribs and skull and spontaneous fracture may occur.

In the past, there has been no agreement among specialists that the plasma cells which proliferate in multiple myeloma are recognizably abnormal. By studying a number of patients at the hospital's General Clinical Research Center, Drs. Bernier and Graham have found that not only is there a recognizable abnormality in cells in multiple myeloma, but that the degree of abnormality also closely parallels the clinical severity of the disease.

A plasma cell consists of two parts, the nucleus and the cytoplasm, which normally mature at the same rate. The scientists discovered that in multiple myeloma, there is a lack of synchronization between the two parts of the

(more)

plasma cell. The nucleus of the multiple plasma cell tends to remain immature, while the cytoplasm develops to maturity.

The investigators are hopeful that their findings will permit definitive treatment to be started in some patients earlier than was previously possible. Currently, Drs. Bernier and Graham are examining the changes which come about through treatment, hoping to determine whether they can predict responsiveness to treatment.

The investigators presented their findings at the meeting of the American Society of Hematology.

#

FIRST QUARANTINE ACT--The first Federal Quarantine Act was passed in 1878. Congress appropriated funds for investigating the origin and causes of epidemic diseases, especially yellow fever and cholera, according to the National Institutes of Health.

FIRST NIH LAB--The National Institutes of Health can be traced to one bacteriology laboratory established in Staten Island, N.Y., during August 1887.

Research Advances

In The Literature:
Lancet, February 9, 1974

HISTAMINE MAY INCREASE BACTERIAL INFECTIONS IN ECZEMA--Inhibition by histamine of the movement of certain white blood cells called neutrophils may explain the frequent occurrence of serious bacterial infections in patients with chronic eczema.

Eczema is an itching, inflammatory skin eruption affecting both children and adults, especially those with family histories of allergic disorders. Patients with the disease seem to be very susceptible to bacterial skin infections causing deep abscesses, suggesting an underlying defect in the immune response.

In studying three children with chronic eczema and recurrent severe staphylococcal and streptococcal infections, Harry R. Hill, M.D., and Paul G. Quie, M.D., of the University of Minnesota Medical School found such a defect when neutrophils of these patients failed to respond to a factor which, ordinarily, causes these disease-fighting cells to migrate to the sites of immunological reactions.

Because histamine, the chemical released when antigen reacts with IgE antibody, has been reported to inhibit chemotaxis (the chemically-induced migration of neutrophils), the scientists decided to determine whether or not histamine might play a role in the infections suffered by the three study patients. They found unusually high levels of IgE, the antibody associated with the release of histamine, in the sera of all three patients. The investigators also observed wheal and flare reactions, indications in the skin of increased release of histamine.

(more)

Histamine (Cont'd)

Additionally, Drs. Hill and Quie found impaired neutrophil chemotaxis in all patients, not only during active skin infection but also during convalescence. To investigate this phenomenon, they incubated normal neutrophils with the patient's sera. No decrease in chemotaxis occurred, therefore eliminating high levels of IgE as the cause of this phenomenon. However, when high concentrations of histamine were added to the mixture of normal neutrophils and patient sera, the response to the chemotactic factor was inhibited.

Drs. Hill and Quie believe that the IgE in the sera of the patients with eczema may be interacting with antigen, or sensitized cells, and releasing large amounts of histamine, thus causing the decreased chemotaxis and susceptibility to bacterial infections. Their work was supported by the National Institute of Allergy and Infectious Diseases.

#

PHS IS NAMED--The Public Health and Marine Hospital Service was officially renamed the Public Health Service (PHS) on August 14, 1912. The same legislation authorized the PHS to conduct field investigations of the diseases of man and the pollution of navigable streams, according to the National Institutes of Health.

Photo Feature

UCLA SCIENTISTS DEVELOP NEW TELEMETRY DEVICES

Scientists at UCLA are using telemetry for the measurement of medically important information such as blood pressure, temperature, cardiogram, and brain waves. These measurements can be taken from a patient many miles away from the doctor who reads and interprets the information.

Ordinarily, measurement of brain waves, important in disorders such as epilepsy in which the person has incapacitating convulsions, are made by connecting the patient to a machine using wires. This is restrictive and bothersome after a short period of time. Instead, the UCLA scientists use radio waves to transmit the patient's brain waves after they have first been sensed by small electrodes pasted to the scalp. The actual device which does the transmitting is not taxing to wear.

Since the patient can lead a more normal existence during this type of monitoring and can walk around freely, he tolerates much longer recording periods.

The UCLA Brain Research Institute doctors also use the telemetry device to monitor children with early infantile autism. Due to the hyperactivity of such children, telemetry has been the only means of obtaining acceptable clinical recordings.

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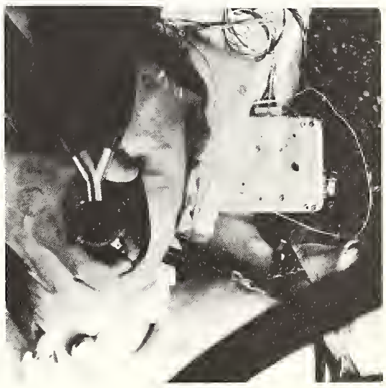
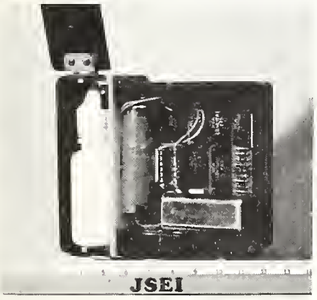


Monitoring by telemetry allows complete isolation between the open heart surgery patient and the recording apparatus. These recordings are safe and are not contaminated by electrical artifacts. (NIH Photo #1303)

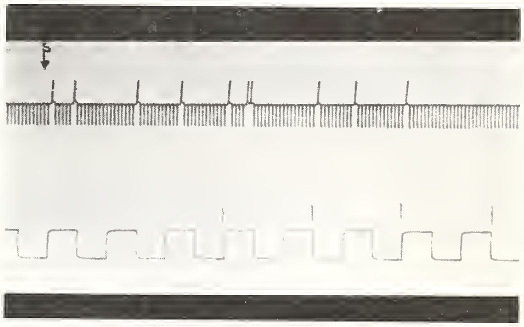
Telemetry (Cont'd)

The UCLA scientists have also developed a miniaturized eight channel telemetry system for obtaining neurobiological data from free ranging monkeys. In a large colony vivarium, each monkey wears a semi-implantable telemeter. Because individual cage collar restraints are eliminated, the animals are free to interact and their neurobiological and behavioral functions more closely resemble that of their natural state. Opportunities to observe aggression and territorial behavior are possible with simultaneous capabilities of recording neuroelectric signals.



Drugs prescribed by a physician must often be taken at fixed time intervals for maximum effectiveness. A telemetry device called the Medication Chronolog was developed by UCLA scientists to automatically perform drug recordkeeping for the patient. It is activated when the patient opens it to take his medication. The lightweight Chronolog (left), approximately the size of a cigarette pack, records for over three weeks. The device was initially developed to assist in the treatment of outpatients with glaucoma and is easily opened by persons with poor eyesight. (NIH Photo #1304)

Oscillographic output of data collected from a Medication Chronolog (right) indicates that the patient did not take the medication at regular intervals as directed. The upper trace indicates opening by an upward mark. The lower trace indicates eight-hour time span. (NIH Photo #1305)



Scientists at the UCLA Laboratory of Environmental Neurobiology, with grant assistance from the National Institute of General Medical Sciences, have designed and developed these telemetry systems.

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Photo Feature

Fighting Cavities...

NIDR TESTS CARIES VACCINE ON MONKEYS

This monkey is not quite sure he wants to accept the peanut butter sandwich the scientist is offering since such snacks contribute to tooth decay. But this is exactly why researchers at the National Institute of Dental Research (NIDR) are tempting him. In exploring the possibilities of a vaccine against dental caries, investigators are working with a breed of Old World monkey, the Macaca fascicularis, *which survives on human-type diets. The monkey's dentition, which is large enough to accommodate normal-size dental instruments, resembles that in humans. Also, many bacteria strains found in the animal's mouth are similar to those detected in man. In the picture below, investigators are shown injecting the killed bacterial strains into the parotid gland of an anesthetized monkey. Preliminary results show that the vaccine, which stimulates the production of salivary antibodies, reduces the amount of* Streptococcus mutans *in dental plaque, the sticky, invisible film that regularly collects on teeth surfaces.* S. mutans *are the bacteria suspected of causing decay in human teeth. Scientists at NIDR say, however, that much research remains before the vaccine can safely be tested in humans. (NIH Photos #1306, 1307)*

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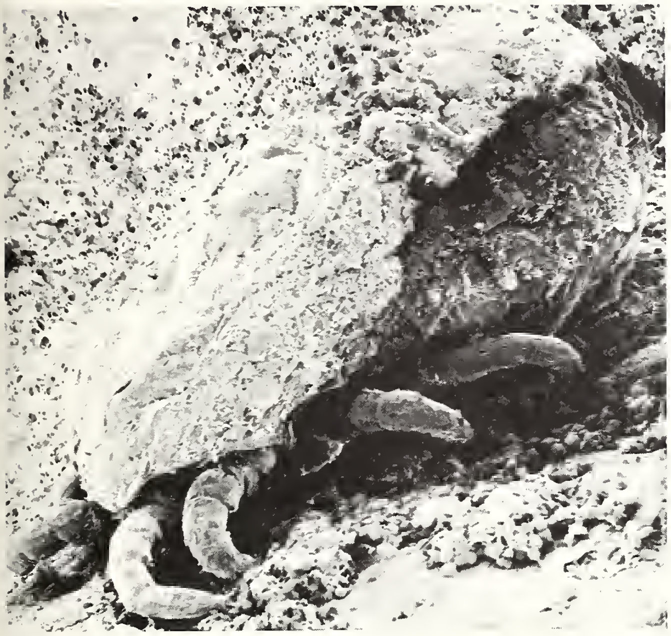
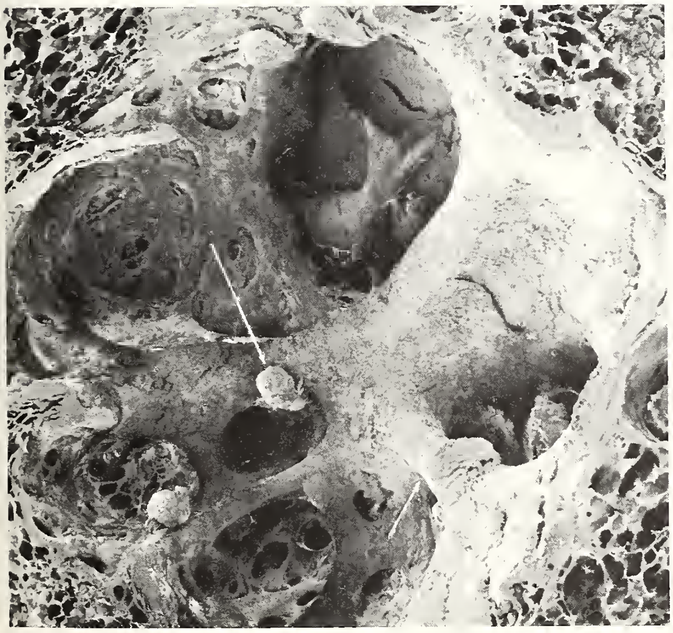
Photo Feature

MITES SET UP "HOUSEKEEPING" IN MONKEYS' LUNG WALL





Lung mites found in wild-caught rhesus monkeys have a crab-like appearance. (Top photo) Using a scanning electron microscope, scientists at the California Primate Research Center are investigating these minute parasites in a study supported by the Division of Research Resources (DRR). Researchers discovered that the mites, which cannot be detected clinically, set up "housekeeping" in lesions known as "mite houses." (Bottom photo) The monkey's lung wall has a thickened, granular appearance caused by a localized inflammatory reaction. The scientists also found that the mite moves slowly in this environment because its surface and legs are covered with inflammatory cells. (NIH Photos #1308, 1309)

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Medical News Tip

ZERO POPULATION GROWTH--A given population reaches Zero Population Growth (ZPG) when the number of births and immigrants equals the number of deaths and emigrants. Thus, the total population neither increases nor decreases. The population of the United States has not reached ZPG. It is growing by 0.7 percent per year. In 1973, the birth rate (15.0 per 1,000) exceeded the death rate (9.4 per 1,000) and immigration exceeded emigration.

This country has, however, now reached fertility rates below the "replacement level." Replacement level fertility occurs when women have only enough children to replace themselves and their husbands (about 2.1 births per woman, on the average). Under these circumstances, in the next generation there will be about one man and one woman in the reproductive ages for each one now living in the reproductive ages.

For information about population dynamics, contact the National Institute of Child Health and Human Development, Landow Building, Room A804, Bethesda, MD 20014, Phone (301) 496-5133.

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New Publication:
The NINDS Multiple Sclerosis Research Program

Multiple sclerosis is one of the most common chronic diseases affecting the human brain and spinal cord. It is characterized by a loss of the fatty sheaths (myelin) that surround the nerve fiber and derives its name from the plaques or patches of scarred (sclerosed) nervous fibers that dot the central nervous system. An estimated 100,000 to 250,000 Americans suffer from the disease.

Multiple sclerosis advances in a series of unpredictable attacks in most patients. In early stages, attacks are more often followed by periods of remission. With successive episodes, resulting scars in the central nervous system become more numerous, more dense, and more destructive, causing progressively severe disability. It should be noted, however, that multiple sclerosis symptoms are not always progressive. Some patients experience one or two episodes and are never bothered again. The disease most commonly strikes women between 20 and 40 years of age.

The cause of multiple sclerosis remains unknown despite the compiling of enormous amounts of information from basic research, clinical studies, and epidemiologic investigations.

The National Institute of Neurological Diseases and Stroke has released an informative new publication, *The NINDS Multiple Sclerosis Research Program*, detailing the multiple sclerosis research now in progress. Science writers can obtain a free copy of this publication from:

NINDS
Building 31, Room 8A-03
Bethesda, MD 20014
Phone: (301) 496-5751

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News Releases Issued

PAP TEST--The National Cancer Institute (NCI) has awarded nine contracts to improve the Pap test for cancer of the cervix. Under the contracts, which have a first year total of $1,670,791, the Pap test will be studied and modified for rapid analysis by automated instruments. With the present technique, cancer may be detected in cells scraped or smeared from the cervix, stained with dyes, and examined under a microscope. Convincing all adult women in this country to have an annual Pap test is a goal of NCI; however, adequate numbers of technicians and laboratories are not available to conduct this volume of testing. One approach to solving this problem is NCI's support of the development of three laboratory instruments for automated analysis of Pap test specimens. The instruments are designed to scan specimens rapidly and select those with abnormal cells for subsequent analysis by trained personnel. The new contracts will investigate preparation of specimens more suited to instrumental analysis than are present Pap smears.

COMPREHENSIVE CENTER--NCI has also announced that Fox Chase Cancer Center and the University of Pennsylvania, both in Philadelphia, are jointly developing a Comprehensive Cancer Center program, as authorized by the National Cancer Act of 1971. This latest comprehensive center program becomes the seventeenth in a new nationwide network of institutions whose purposes are to conduct a broad range of cancer research and to develop and demonstrate the best method of cancer prevention, diagnosis, treatment, and rehabilitation.

FLUORIDE--A project to develop a system of prolonged release of fluoride in

(more)

the mouth as a means of fighting tooth decay is being initiated under a one-year contract from the National Institute of Dental Research and Polysciences, Inc. of Warrington, Pennsylvania. Different methods of releasing fluoride will be studied over a 12-month period. Scientists will try to find a biologically suitable system which will supply fluoride in the mouth at a constant, predetermined rate for a period of at least six months without maintenance or adjustment. The specific methods to be explored include incorporating a safe fluoride salt into a matrix of some soft, rubbery, plastic polymer; covering such a salt with a plastic membrane that permits it to dissolve only at a constant, slow rate; developing a fluorophosphate compound that will break down in the moisture of the mouth and release fluoride gradually; or covering such a compound with a membrane to insure slow release. Also, the scientists will try adding fluoride to a gel and containing the mixture with a plastic membrane to control dispersal.

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October 25, 1974

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NEWS & FEATURES From NIH October 25, 1974

HEPATITIS OCCURS FREQUENTLY AMONG HOSPITAL ANESTHESIOLOGISTS

Hepatitis occurs more frequently in anesthesiologists than in other health care personnel.

Investigators in Boston have found a history of hepatitis in 20 percent of the members of the anesthesiology department at Massachusetts General Hospital, a rate two and one-half times that found in health care personnel and five times higher than that for individuals in other professions not working in hospitals.

The frequency of hepatitis B antigen (HBAg) and antibody (HBAb) among health care personnel has been fairly well investigated. Recently, preliminary reports from the American Society of Anesthesiologists suggested that anesthesiologists had a higher frequency of hepatitis than other physicians. Based on this finding, Alix Mathieu, M.D., and associates designed the present study to assess the frequency of hepatitis in a large group of anesthesiologists, to establish the incidence of HBAg and Ab carriers in this population, and to investigate the possible correlation between previous history of hepatitis in these individuals and their carrier state for HBAg or HBAb.

The study population consisted of 70 individuals (53 males and 17 females). The investigators used questionnaires to determine the degree of specific exposure to hepatitis B (HB) positive blood or to hepatitis A (HA). From each person in the study group, the investigators then took ten milliliters of blood and tested it for HBAg by solid phase radioimmunoassay (RIA) and counterimmunoelectrophoresis (CIEP) and for HBAb by CIEP and radioimmuno-

(more)

precipitation (RIP). If the specimens were found to be antigen or antibody positive, liver function tests were performed.

The potential risk of infection in this population arises from handling of blood, from carrier patients infected with the hepatitis virus, and from needle pricks. Most anesthesiologists could not establish exposure to hepatitis from the handling of blood products, because most of the blood used in the operating room is pre-screened. The incidence of needle prick in the group is reported at 96 percent, while the incidence of HBAg positive and HA infections in the families of those studied was negligible in 60 percent and unknown in 40 percent. The incidence of other known contacts was 93 percent.

Dr. Mathieu and colleagues found it surprising that no carriers were found by RIA--the most sensitive assay now available--especially in light of the increased incidence of hepatitis in the group.

They explain that in the eight individuals HBAb positive by RIP, three had a previous history of hepatitis B or A and all had known contacts. In the remaining five people, this positivity might be due to multiple transfusions (in one person) and long-term or close contacts with a relative with known hepatitis. Liver function tests in these eight individuals were normal. The infectivity of HBAb positive blood has not yet been determined, but these individuals are not accepted as blood donors.

According to the investigators, their results demonstrate the lack of sensitivity of the CIEP method--the conventional hospital method--for detecting antibodies. This lack of sensitivity may lead inadvertantly to such people being accepted as blood donors.

(more)

Hepatitis (Cont'd)

Dr. Mathieu presented these findings on October 15, 1974 at the meeting of the American Society of Anesthesiologists, Washington, D.C. Associated with him in the study were: George E. Battit, M.D., Charles Huggins, M.D., and Richard J. Kitz, M.D., of Harvard University and the Massachusetts General Hospital; and Robert H. Purcell, M.D., senior investigator and head of the Hepatitis Virus Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases. Dr. Kitz is a grantee of the National Institute of General Medical Sciences.

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LIBRARY BEGINS--The National Library of Medicine, a bureau of the National Institutes of Health, was established in 1836 as the Library of the Office of the Surgeon General of the Army, according to the National Institutes of Health.

MARINE HOSPITAL SERVICE--President John Adams established the Marine Hospital Service on July 16, 1798. This service, originally created for the relief of sick and disabled seamen, developed into today's Public Health Service, according to the National Institutes of Health.

Research Advances

CANCER SCIENTISTS DISCOVER CAUSE OF RARE IMMUNE-DEFICIENCY DISEASE

National Cancer Program scientists have discovered the cause of a rare immune-deficiency disease that sometimes leads to cancer, and in so doing, have uncovered new information on the workings of the body's system of defenses against many diseases.

For several years, Thomas A. Waldmann, M.D., and colleagues at the National Cancer Institute (NCI) have studied patients, primarily children, with a life-threatening disease called common variable hypogammaglobulinemia (CVH), which is characterized by the patient's inability to manufacture protective antibodies. Fifty patients with the disease have been treated in the NIH Clinical Center, and all such patients have recurrent severe infections, particularly pneumonia. Most of the victims also develop other lung diseases; thirty percent develop arthritis; ten percent, cancer.

After a series of experiments, the investigators discovered that the patients' immune defect was due to an excess of a certain type of T-lymphocytes, the white blood cells that originate in the bone marrow and migrate through the thymus (T) gland before becoming active immune agents. Dr. Waldmann and his colleagues found that the type of excessive T-lymphocytes in these patients were "suppressor" T-cells.

Another subgroup, "helper" T-cells, assist mature B-cells (another class of white blood cells) in antibody production. An excess of "suppressor" T-cells, the NIH scientists found, blocks antibody production by the B-cells It is this defect that weakens children with CVH and makes them vulnerable to infections and other diseases.

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The scientists grew lymphocytes from 13 patients with CVH in laboratory cultures and found that, despite chemical stimulation, they produced from 16 to 37 times fewer antibodies of each of three important classes (IgG, IgA, and IgM) than lymphocytes from normal individuals under the same test conditions. Additionally, during repeated cell culture tests, B-cells from normal persons produced eight to ten times fewer antibodies when lymphocytes from CVH patients were added to the cell cultures. Co-culturing of cells from unrelated normal individuals did not result in any significant reduction in antibody production.

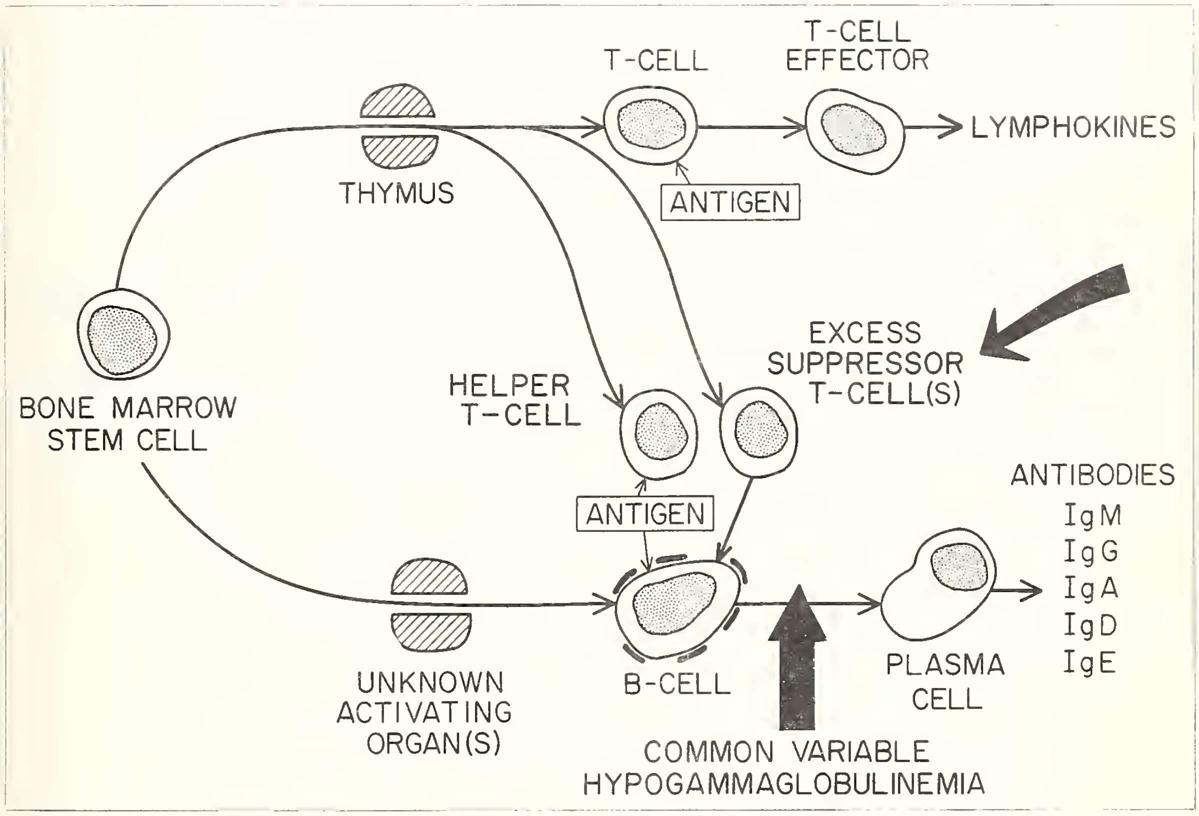
The excessive numbers of suppressor T-cells in CVH patients prevent their B-cells from maturing into fully competent antibody-producing cells (plasma cells), according to Dr. Waldmann. The findings may also have relevance in other diseases associated with abnormal antibody production. In systemic lupus erythematosus, for instance, a lack of suppressor T-cells may be the cause of runaway antibody production, creating antibodies against the patient's own normal tissues and organs. Chronic lymphocytic leukemia and cancers of the thymus and bone marrow may also be associated with T-cell imbalances.

The research, conducted by Dr. Waldmann, Samuel Broder, M.D., Mary Durm, Marcia Blackman, R. Michael Blaese, M.D., and Warren Strober, M.D., of the NCI Metabolism Branch, was reported in the September 14, 1974 issue of *Lancet*.

The existence of suppressor T-cells was reported in 1970 by Phillip J. Baker, Ph.D., of the National Institute of Allergy and Infectious Diseases. Research at Yale and Harvard Universities, and the National Institute of

(more)

Arthritis, Metabolism, and Digestive Diseases also provided background information contributing to this new understanding of the nature of common variable hypogammaglobulinemia. The current findings, in turn, help to delineate some of the mysteries of the entire immune system.



This is a schematic drawing of the complex mechanism of antibody failure in common variable hypogammaglobulinemia (CVH). The large arrow at bottom indicates blockage in normal B-cell maturation into antibody-producing plasma cells. NIH scientists postulate that normal persons are capable of producing adequate amounts of "helper" and "suppressor" T-cells in response to disease agents, or antigens. Abnormal "suppressor" T-cell production adversely affects B-cell maturation; excessive numbers of "suppressor" T-cells are conclusively linked to CVH. B-cells and T-cells are believed to originate as primitive stem cells of the bone marrow. Other immunologic factors in the body's defense are lymphokines, e.g. interferon, lymphotoxin, and macrophage-inhibiting factor, which assist in the rejection of grafts and in normal delayed hypersensitivity reactions. (NIH Photo #1310)

#

Research Advances

SELF-ADMINISTERED QUESTIONNAIRE DISTINGUISHES CORONARY PATIENTS

A self-administered questionnaire is capable of distinguishing between a group of recent coronary heart disease (CHD) patients and a group of controls, according to a retrospective study at the Bridgeport (Connecticut) Hospital. Use of such a method of identifying the coronary behavior pattern may lead to insight on how a certain life style might be associated with a person's health.

During the past 15 years, much emphasis has been placed on certain social and psychological factors suspected of playing a role in coronary atherosclerosis and myocardial infarction. Among the more promising approaches relating behavior to coronary heart disease risk has been the development of the Behavior Pattern Type A by Meyer Friedman, M.D. and Ray H. Rosenman, M.D. of San Francisco. This pattern is characterized by attributes such as hard-driving effort, competitiveness, aggressiveness, impatience, restlessness, striving for achievement, and an intense dedication to one's job. The classification calls men at increased risk to CHD as Type A's; those at lower risk, Type B's.

In the past, three research groups have shown this behavior pattern to be associated with increased prevalence of CHD, and with the incidence of CHD (in the Western Collaborative Group Study). The classification of men in these studies has been through the use of standardized interviews interpreted clinically.

In an effort to develop a more quantitative, less expensive, and quicker procedure for judging Type A personalities, C. David Jenkins, Ph.D.,

(more)

of Boston University, in collaboration with Drs. Friedman and Rosenman, developed a self-administered, computer-scored questionnaire called the Jenkins Activity Survey for Health-Prediction (JAS). Dr. Jenkins is a grantee of the National Heart and Lung Institute.

In the present study, Dr. Jenkins and associates used the JAS to study a sample of male and female patients, between the ages of 22 and 64 years, at Bridgeport Hospital, with and without coronary heart disease. Since 23 percent of the sample were women, this provided the first opportunity to evaluate JAS scale scores for both sexes. In addition to the Type A Scales, the investigators scored three dimensions: the first, labeled Speed and Impatience, deals with time urgency; the second, Job Involvement, expresses the degree of the demands and dedication to a job; the third, Hard-Driving, involves perceptions of one's self as being competitive and serious. They also evaluated the tests in terms of several demographic variables.

The results from the 48 CHD patients and 42 controls, show that the CHD cases scored more in the Type A direction than controls on all scales except job involvement. As predicted, the CHD cases exhibited more Type A behavior and were more hard-driving. While there was a trend for the cases to respond with more speed and impatience, the scale did not show a statistically significant difference. Both cases and controls scored low on job involvement, lending support to the idea that during a serious illness, persons are likely to be less committed to the pursuit of their vocations.

According to the investigators, the most significant aspect of the Bridgeport results is the fact that they are consistent with those obtained

(more)

in the Western Collaborative Group Study. This cross-validation, therefore, lends support to the theory underlying the determination of the behavior pattern and further documents the usefulness of the JAS as an objective measure of this personality.

Another important finding was the absence of meaningful differences between men and women on the JAS. Women CHD patients scored higher than women controls on both the Type A and hard-driving scales as did the men.

The investigators also report that the demographic variables of marital status and religion were not important in interpreting the case/control differences, nor were there significant relationships found with JAS scales. Coronary disease patients were more often currently married than controls (85 percent versus 64 percent), but marital status was not found to be significantly associated with JAS scores. Currently married patients (75 percent of the sample) tended to score somewhat more in the Type A direction than those currently nonmarried.

Catholics, distributed nearly equally in both groups, tended to score somewhat lower on the Type A scale and slightly higher on the hard-driving scale than the other religious groups, but none of these associations were statistically significant.

Dr. Jenkins and his associates emphasize that their study was retrospective and that selective bias should be considered in interpreting the results. Also, it is possible that CHD patients attribute to themselves more of the Type A and hard-driving traits than really existed in their pre-illness behavior. The question of whether the behavior preceded the emergence of clinical CHD or followed the illness remains unresolved.

(more)

Coronary Patients (Cont'd)

Dr. Jenkins' colleagues were Daniel Kenigsberg, Wesleyan University, Connecticut; Stephen J. Zyzanski, Ph.D., Boston University; Walter I. Wardwell, Ph.D., University of Connecticut, Storrs; and A. Thomas Licciardello, M.D., Bridgeport Hospital. A report of the work appears in *Psychosomatic Medicine*, July-August 1974.

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HEREDITARY DISEASES--More than 1,800 hereditary diseases have been described in man, according to the National Institutes of Health.

MALNUTRITION--Animal studies have clearly shown that severe malnutrition can slow brain growth and impair behavioral patterns and learning ability, according to the National Institutes of Health.

Photo Feature

University of Connecticut...

MEDICAL LIBRARIANS ACCOMPANY PHYSICIANS ON MEDICAL ROUNDS

Medical librarians now accompany teaching physicians and medical students on rounds in hospitals linked with the University of Connecticut Health Center. The librarians later supply reading material related to what they have seen and heard on rounds.

By actually going on rounds, the librarians can answer direct requests from doctors and students for articles and determine if other material would also be helpful. This makes the information flow user-oriented rather than subject-oriented, according to Gertrude Lamb, Ph.D., principal investigator for the project. Dr. Lamb is director of libraries at the hospital and assistant librarian at the University of Connecticut Health Center.

(more)

Medical librarian Ann Jefferson (left) listens in on rounds conducted by Dr. Robert Harris (right), an attending pediatrician at Hartford Hospital. Such "eavesdropping" enables her to determine what literature may be useful to supplement or reinforce knowledge gained by medical students, interns, and residents. (NIH Photo #1311)

Librarians (Cont'd)

These specialists in medical literature compile reading material from several fields, allowing the physician who specializes in one area of medicine to see articles from other fields of medicine that he normally would not see.

One of the goals behind the program, which will be tested for two years under a grant from the National Library of Medicine, is to improve the young physician's ability to find library material so he or she can eventually find answers to questions independently.

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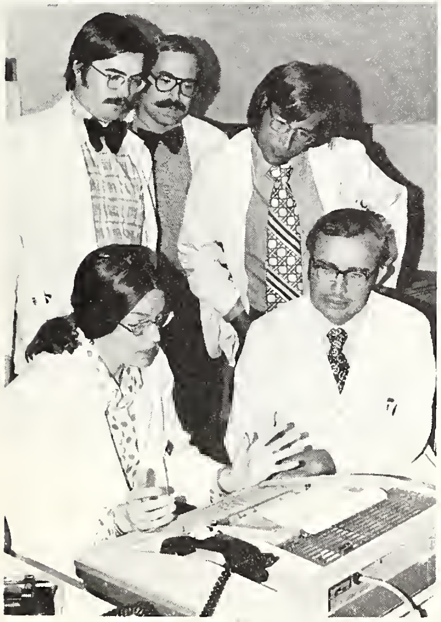


Ms. Jefferson discusses the operation of a Medline terminal with physicians, residents, and medical students at Hartford Hospital (left photo). She also listens to teaching sessions for student nurses (bottom photo) in the hospital's pediatric intensive care unit. Another clinical librarian, Cathryn White (shown on cover page) is assigned to the hospital's emergency and surgery departments. (NIH Photos #1312, 1313)

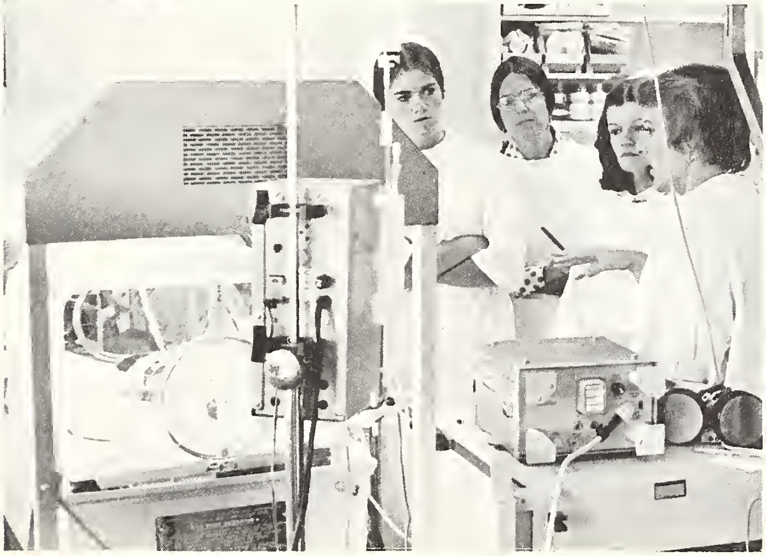
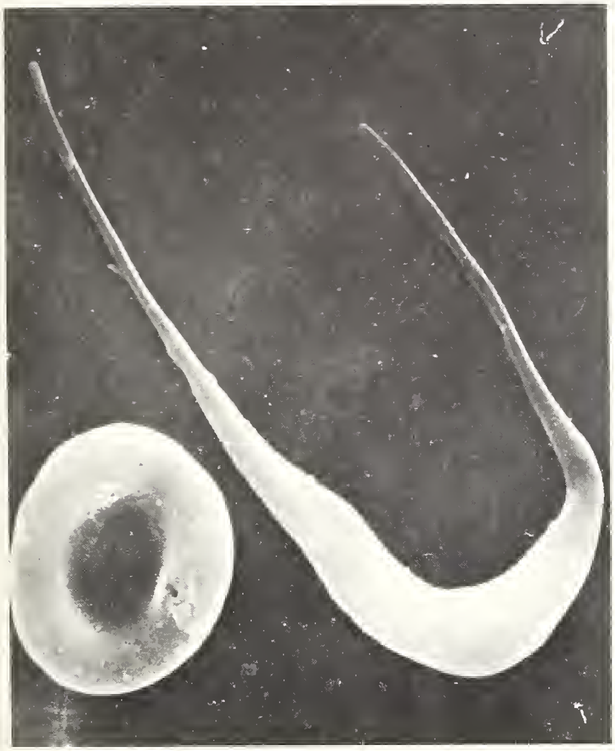


Photo Feature

FLORIDA SCIENTISTS PHOTOGRAPH NORMAL AND SICKLE BLOOD CELLS



Two Papanicolaou Cancer Research Institute scientists took this electron photomicrograph of a normal blood cell and a sickle cell. Bruce F. Cameron, M.D., Ph.D. (left), and Robert M. Zucker, Ph.D. (right), are studying blood diseases and sharing their findings with Donald R. Harkness, M.D., director of the University of Miami Comprehensive Sickle Cell Center. The National Heart and Lung Institute funds 15 Sickle Cell Centers in the United States. (NIH Photos #1314, 1315, 1316)

#

Photo Feature

BABY MONKEYS FIND DOGS CAN BE FOSTER MOTHERS

Research shows that mongrel dogs can readily serve as mother surrogates for baby rhesus monkeys.

William A. Mason, Ph.D., a grantee of the National Institute of Child Health and Human Development, and M.D. Kenney, studied eight immature monkeys that were originally attached to cloth surrogates or other monkeys. When separated from these mother figures and exposed to dogs as substitutes, all eight formed a parental attachment to the canine. Dr. Mason is working at the California Primate Research Center, one of seven primate centers supported by the Division of Research Resources.

Four monkeys were raised from birth to ten months with cloth surrogate mothers, two were with their own mothers from birth until three months of age, and the other two were raised with peer monkeys in enclosed cages until seven months.

The investigators separated the babies and placed them with canine foster mothers. Initially the monkeys reacted to the dogs with fear expressed in grimaces, crouching, distress vocalizations, and withdrawal. Yet within two hours seven of the eight approached the new parent, the eighth approached within seven hours. After four hours, seven monkeys were clinging to their mother surrogates.

The relationship culminated in continuous cohabitation in outdoor kennels where the monkeys and dogs were in frequent contact. Both animals showed the basic features of attachment behavior. The canines groomed and licked the babies; the monkeys clung to the dogs. When the mother surrogates

(more)

Dogs (Cont'd)

were taken from the monkeys for an exercise period, the monkeys became greatly agitated. When the dogs returned, the monkeys quickly picked out their own "mother" from among the other canines.

In cases where the monkeys were originally raised with other monkeys, tests proved that they consistently preferred the familiar dog over the original cage mate or unfamiliar young monkeys.

The findings also showed that when the monkeys were separated from their original dogs and housed with new mother surrogates, the new dog became an effective parent substitute. The scientists feel that a prior bond does not preclude any formation of a new attachment.

When the monkeys were given a choice between an unfamiliar dog and an unfamiliar inanimate surrogate, the strange dog was chosen first in most of the tests.

This dog serves as a surrogate mother to this baby rhesus monkey at the California Primate Research Center, Davis. The NIH Division of Research Resources funds seven primate centers in the United States. (NIH Photo #1317)

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Medical News Tip

SUDDEN INFANT DEATH SYNDROME--In the United States, the Sudden Infant Death Syndrome (SIDS) is the leading cause of death in infancy after the first month of life. In the majority of cases, the baby is apparently in good health, is put to bed for a nap or for the night, and several hours later is found dead. Why these babies die is unknown. Many reasons have been offered to explain the death. Some scientists have theorized that the changed cardiac rate during sleep is one of the causes. But no theory to date has explained it fully. All factors believed to be associated with the syndrome appear to be intertwined.

The National Institute of Child Health and Human Development (NICHD) has an organized, targeted research program to learn more about the causes of SIDS and to find means of preventing it. All SIDS deaths are now recorded on one special code. Training films have been created and regional conferences organized to educate professional and community health workers about SIDS and its aftermath. Voluntary organizations within communities have gone far to support families of SIDS victims and to educate the general public and specific community groups about the syndrome.

There are some promising research leads in finding the causes of SIDS and means of preventing it. Some scientists, for example, believe it may be possible to identify babies at risk before they become SIDS victims. These babies, theoretically, could be closely monitored electronically until they have "outgrown" the period--one month to one year--in which they are at risk.

For information about SIDS, contact NICHD, Landow Building, Room A804, Bethesda, MD 20014, Phone (301) 496-5133.

#

New Publication:
Rocky Mountain Spotted Fever

Rocky Mountain spotted fever is caused by one of a group of organisms known as rickettsiae, which are structurally related to bacteria but, in some of their properties, resemble viruses. The spotted fever agent, *Rickettsia rickettsii*, is transmitted by the bite of a tick, and produces an inflammation of the inner lining of the blood vessels. This inflammation is eventually visible in the form of a rash comprising many red spots under the skin.

The appearance of this rash on the wrists and ankles is one of the main clues used by doctors to diagnose spotted fever. The rash is preceded, however, by several days of chills, high fever, headache, and bone pain.

The National Institute of Allergy and Infectious Diseases has released a new publication, *Rocky Mountain Spotted Fever*, relating the history of the research which has produced both a cure for the disease (in the form of antibiotics) and a vaccine which is recommended for persons working in high-risk occupations--rickettsiologists and their technicians, for example.

Science writers can obtain a copy of this publication from:

NIAID
Building 31, Room 7A-32
National Institutes of Health
Bethesda, MD 20014

#

News Releases and Announcements Issued

FELLOWSHIPS--The Swedish Medical Research Council will make available in 1975 three research fellowships in basic or clinical sciences related to health to qualified biomedical scientists who are American citizens. Candidates must have a doctoral degree and be engaged in independent research. Fellowships will run for 12 months and the award will cover payment of a stipend and transportation expenses. An NIH committee will review applications and forward nominations to the Swedish Medical Research Council. The deadline for receipt of applications is January 31, 1975. Final selection will be made in May 1975. Further information can be obtained from Dr. Eugene L. Walter, Jr., Fogarty International Center, Bldg. 31, Room 2B-59, NIH, Bethesda, MD 20014, Phone (301) 496-1443.

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Research Advances

Viral Infection...

NEW INTERFERON INDUCER PROTECTS NON-HUMAN PRIMATES

Scientists have developed a new chemical complex which induces a high level of interferon in monkeys or chimpanzees and protects them prophylactically against a lethal virus. Therapeutic trials in non-human primates are planned with the hope that the new chemical will eventually prove useful in preventing or treating viral infections and malignancies in humans.

Interferon is a protective substance produced naturally by the body in response to attack by viruses and some other intracellular parasites. For a number of years, scientists have been studying the ability of interferon to assist in an animal's recovery from viral infection and have been searching for ways to enhance interferon production.

The synthetic ribonucleic acid, poly I.poly C, an effective interferon inducer in rodents, also protects these animals against certain viral infections and malignancies. Poly I.poly C is not useful in man, however, possibly due to its susceptibility to the destructive action of certain enzymes in human serum.

The new chemical is a complex of high molecular weight poly I.poly C, low-molecular weight poly-1-lysine, and a stabilizer (carboxymethylcellulose). Its composition was worked out by a team of scientists led by Hilton B. Levy, Ph.D., of the Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases (NIAID).

Assays showed the new chemical complex--poly I.poly C, poly-1-lysine--to be four to 10 times more resistant than poly I.poly C to the destructive action

(more)

of human serum. Furthermore, the new complex induced high levels of interferon when injected into monkeys or chimpanzees. At the doses used, no toxicity was noted.

In several experiments, the poly I.poly C, poly-1-lysine complex was injected into Rhesus monkeys prior to challenge with a lethal dose of Simian hemorrhagic fever virus. Most of the treated animals developed no disease. Only one developed disease, two weeks after challenge, but recovered following additional treatment with the chemical complex. All of the control animals (untreated before virus challenge) were dead in seven to eight days, a common response to Simian hemorrhagic fever virus. Comparable results have been obtained in experiments involving yellow fever virus in monkeys and the new interferon inducer.

Dr. Levy's associates in these experiments were George Baer, D.V.M., Center for Disease Control, Atlanta; Samuel Baron, M.D., and Michael Iadarola, NIAID; Clarence J. Gibbs, Jr., Ph.D., and William T. London, D.V.M., of the National Institute of Neurological Diseases and Stroke; Jerry M. Rice, Ph.D., National Cancer Institute. The results of the studies were presented at the 1st Intersectional Congress of the International Association of Microbiological Societies, Tokyo, September 1-7, 1974.

#

Research Advances

INVESTIGATORS SYNTHESIZE CELL WALL IN TEST TUBE

Scientists working at the University of California, Riverside, have achieved synthesis of yeast cell wall fragments in a test tube for the first time. This accomplishment adds much to the understanding of cell wall manufacture and brings closer the possibility of assembling an entire wall in the absence of intact cells.

J. Ruiz-Herrera, Ph.D., and S. Bartnicki-Garcia, Ph.D., performed their study with cell membrane fractions of the yeast form of the fungus *Mucor rouxii*. The yeast's wall-manufacturing enzyme, chitin synthetase, is associated with the membranes, and the scientists hypothesized that the enzyme would be liberated by exposure of this fraction to the basic substance of which *M. rouxii* cell walls are composed, that is, the enzyme's substrate.

The investigators' hypothesis proved correct. Addition of the substrate, along with an "activator", at 0°C., caused about 15-20 percent of the enzyme activity to become soluble. When the soluble enzyme was subsequently brought to room temperature, fibrous material precipitated out of solution. Chemical and electron microscopic examination of this product revealed that it was composed of tiny filaments (microfibrils) of the polysaccharide chitin, similar to the *M. rouxii* wall. Thus, for the first time, the scientists demonstrated assembly *in vitro* of normally constructed microfibrillar wall.

In addition to proving that cell wall microfibrils can be formed in the absence of living cells, these results support the belief that formation of wall microfibrils takes place at the cell surface rather than within the cell.

(more)

Cell Wall (Cont'd)

Dr. Ruiz-Herrera and Bartnicki-Garcia reported their findings in the October 25, 1974 issue of *Science*. Dr. Ruiz-Herrera is on leave of absence from the Instituto Politecnico Nacional, Mexico. Dr. Bartnicki-Garcia is professor of Plant Pathology, University of California, Riverside. This study was supported by a grant from the National Institute of Allergy and Infectious Diseases.

#

ALLERGIES--Approximately 17 out of every 100 Americans--or 35,277,000--suffered from one or more major allergies last year, according to the National Institutes of Health.

OVERNUTRITION--Overnutrition is as much a concern to the American people as is undernutrition, for about one-sixth of the country's population is overweight, according to the National Institutes of Health.

Research Advances

In The Literature:
Oral Surgery, Oral Medicine, Oral Pathology, January 1974

ALLOGENEIC BONE MATRIX SOLVES PROBLEMS OF BONE GRAFTS--Two problems common to most bone grafts--ankylosis and loss of growth--appear to be solved by using decalcified allogeneic bone matrix.

In previous research National Institute of Dental Research grantees Herbert Wells, D.M.D., of Boston University, and Ramesh Narang, D.Sc.D., now at the University of Louisville School of Dentistry, Kentucky, showed that cortical bone decalcified in 0.6N hydrochloric acid for 24 hours could be stored and used when needed to repair many types of bone defects in unrelated animals of the same species. The bone matrix is soft and easily carved to fit the desired shape. There is no inflammation from the graft and the matrix material is not rejected. Instead, it stimulates new bone to form and gradually replace the slowly resorbing matrix.

Drs. Wells and Narang found that their matrix preparations, which work in rats, dogs, and now in monkeys, have uses other than filling gaps in long bones or producing new alveolar ridges, as previously reported. However, the bone must be allogeneic (that is, derived from the same species) not xenogenic (from a different species).

Recently, the scientists successfully repaired surgical defects in the hard palates of dogs and monkeys, and even replaced joints (head of the fibula) in adult rats and the ball of the jaw hinge (condyle of the mandible) in newborn rats. Joints are especially difficult to repair because they tend to ankylose or fuse so that motion is limited, or to develop fibrous tissue where bone is needed for strength. The condyle is even more of a problem

(more)

because it is the chief growth center of the lower jaw. Operations on the condyle in youth are likely to hinder growth and result in a lopsided appearance of the adult.

The investigators found that the jaws of their day-old rats grafted with condyles of bone matrix, after the removal of their own condyles, grew quite normally compared to those that had condyles removed and not replaced. However, the grafted side was slightly shorter than the undisturbed side.

This research is of particular interest because disorders of the condyle in human beings, which fail to respond to conservative treatment, frequently require surgical intervention which often results in undesirable side effects such as ankylosis and loss of growth. Allogeneic bone matrix does not evoke any immunologic response, therefore a second surgical procedure on the same patient to obtain homogeneic graft material is also eliminated.

#

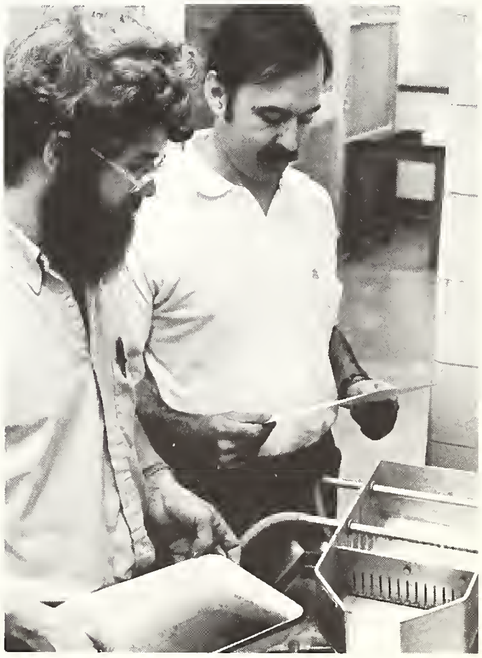
Photo Feature

NIAID INVESTIGATES MALARIA CONTROL

Researchers at the National Institute of Allergy and Infectious Diseases (NIAID) are studying a biological method for controlling the transmittal of malaria by mosquitoes. Robert W. Gwadz, Ph.D., head of the insectary in NIAID's Laboratory of Parasitic Disease, is investigating the *Anopheles* mosquitoes to genetically control their vector capacity. The two vector species under study--*Anopheles balabacensis* and *A. maculatus*--will not mate in captivity. In order to maintain these species, Dr. Gwadz must rely on forced mating, a technique developed by William E. Collins, Ph.D., head of NIAID's former Malaria Unit in Chamblee, Georgia. With increasing world travel, control of malaria is becoming vitally important to the entire world, particularly to those living in endemic areas.

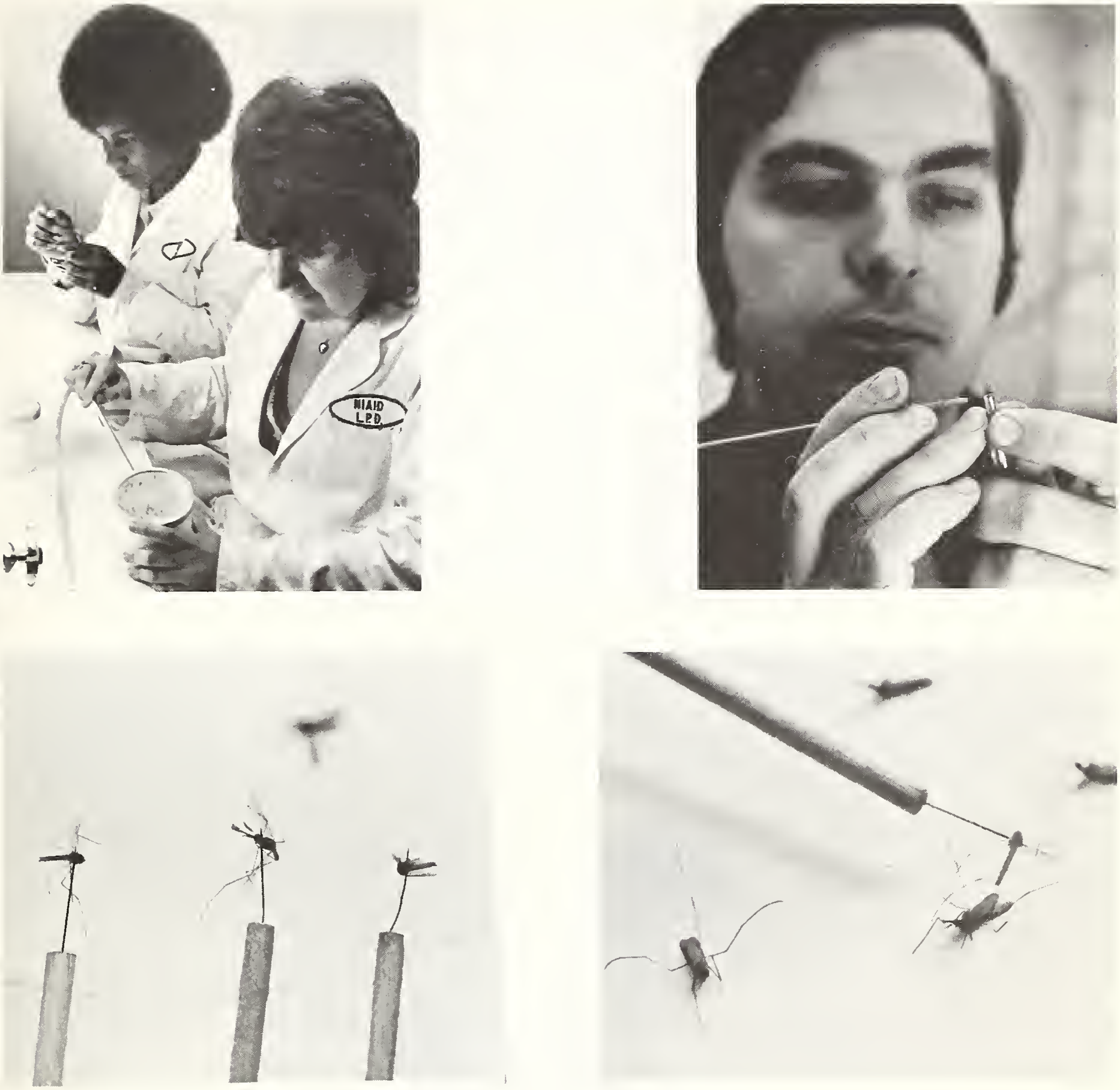
(more)

Dr. Gwadz inspects a cage containing hundreds of Anopheles *mosquitoes. If he is able to place these malaria breeders under simple genetic control, stocks of mosquitoes completely resistant to the parasite could be developed through a selective breeding process. (NIH Photo #1318)*



Entomologist Doug Seeley, right, and biologist Chris Ankrom use an automatic pupae separator, which distinguishes infant male mosquitoes from the larger females by size. (NIH Photo #1319)

Malaria (Cont'd)



Mosquitoes are prepared for the forced mating (top left). Paddy Sigmon (left), anesthetizes females with ether while Rose Hess, using a vacuum apparatus, catches males. Male mosquitoes (top right photo) literally lose their heads over females. Dr. Gwadz performs radical brain surgery, impaling a male on a needle, and removing the head. The nerve center which controls the mating instinct is located in the head and removal releases the male mosquito's inhibitions. The bottom left photo shows the stag line! Which one of these lucky males will mate with the beauty in the background? Although some males have already lost their heads, each of them is ready to impregnate a female. A female mosquito can be impregnated only once. The male mosquito (bottom right photo) is gently placed on the anesthetized female and it is consummated! The optimum mating age for the female is four days while that of the male is eight days. (NIH Photos #1320, 1321, 1322, 1323)

(more)

Malaria (Cont'd)

Containers of Anopheles *mosquitoes infected with malaria are isolated in one of the insectary's breeding rooms where light, temperature, and humidity are controlled. Two of the parasites which these mosquitoes transmit--*Plasmodium falciparum *and* Plasmodium vivax*--will be maintained in the insectary's colony of rhesus and owl monkeys. (NIH Photo #1324)*

Entomologist Nancy Watkins dissects female mosquitoes under the microscope and checks for the presence of malarial oocysts in their stomach linings. Oocysts contain a form of the parasite--sporozoites--which eventually reach the mosquito's salivary glands and with the next blood meal are injected into the host. This blood is needed by the female mosquitoes--the only ones biting humans--in order to manufacture eggs. (NIH Photo #1325)

#

News Feature

EARLIER DETECTION, IMPROVED TREATMENTS HELP LUNG PATIENTS

Respiratory failure may occur in many disorders, both acute and chronic, pulmonary and nonpulmonary, according to the National Heart and Lung Institute (NHLI).

Despite considerable progress in the development of sophisticated therapy, respiratory distress syndromes (RDS) in adults remain among the most common causes of postoperative mortality and of death related to major trauma. However, the syndromes are potentially reversible if recognized early and treated promptly and properly. The NHLI research emphasis, therefore, is on identification of factors that predispose patients to RDS, studies of the effects of oxygen toxicity, and development of therapeutic devices, especially ventilatory assist devices and oxygenators.

Various techniques and devices have been developed for the detection of potential respiratory failure. A sensitive spirometer that measures the peak acceleration which occurs early in forced expiration is now being evaluated for its ability to detect early airway obstruction. Also, methods have been developed and are being evaluated for assessment of the degree of pulmonary edema. Powdered tantalum, as a roentgenographic contrast medium, has been clinically used to study the structure and function of bronchi, bronchioles, and alveoli in diseased lungs.

In addition to achieving earlier detection of potential respiratory failure, scientists hope to develop monitoring devices and modes of therapy that are less costly, less complicated to administer, and more readily available than those now in use. A welcome development would be a portable,

(more)

rugged, reliable mass spectrometer for continuous measurements of respiratory gases. Also needed are microsized, reliable, stable electrodes for the continuous *in vivo* gas measurements of pO_2 and pCO_2. Another challenge is obtaining a more complete assessment of changes in pulmonary function and structure during respiratory failure.

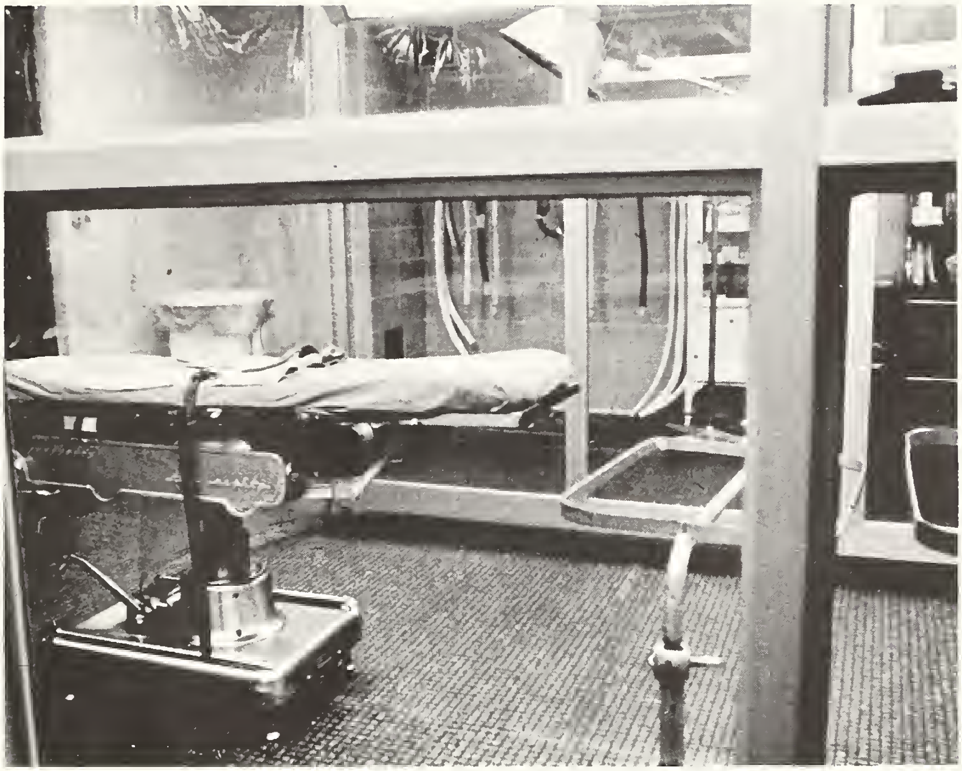
The development and evaluation of new noninvasive monitoring devices are required to support the therapeutic measures provided in critical care settings. A newly-developed technique to continuously measure the ventilation/perfusion ratio may provide an important contribution. Another hope for better lung function monitoring lies in new lung imagery techniques.

The current basis for therapy during RDS is respiratory support with positive pressure and high oxygen concentration. However, NHLI wants to know more about the long-term effects on the lungs of high oxygen concentrations and continuous mechanical ventilation.

Lung diseases, including RDS, account for about 150,000 American deaths each year. Other annual costs of lung diseases to the nation include 60 million days lost from work, 40 million days of bed-restricted activity, and six billion dollars in lost productivity, reduced wages, and added medical care costs.

Photo Feature

ORTHOPEDIC SURGERY STUDIED IN SPECIAL OPERATING ROOM



This "germ-free" surgical suite (above) at the University of Tennessee Center for the Health Sciences, Memphis, was designed by Lewis D. Anderson, M.D., to use in surgery for bone infarcts and total hip replacement. The room air is carefully controlled, and hospital personnel must wear special helmets (left). Dr. Anderson, a professor of orthopedic surgery, uses the suite to study orthopedic aspects of sickle cell disease. His research is supported by the National Heart and Lung Institute. (NIH Photos #1326, 1327)

#

Medical News Tip

HYPERBILIRUBINEMIA--Many infants, whether low birth weight or full term, become jaundiced in the first few days of life from the over-production or under-secretion of bilirubin, a breakdown product of hemoglobin and heme substrates in the infant. The excess of bilirubin in the blood is called hyperbilirubinemia. When aggressive treatment is indicated, it is sometimes exchange transfusions or in some milder cases, a newer method called phototherapy (or light therapy).

Although the precise biochemical transformation mechanism is not yet known, researchers have found that phototherapy changes bilirubin into an excretable form. Patches are often used to protect the infant's eyes and then the baby is placed under special lights for several hours or even a few days. Frequent blood sampling is part of the patient monitoring system.

For more information about hyperbilirubinemia, contact the National Institute of Child Health and Human Development, Landow Building, Room A804, Bethesda, MD 20014, Phone (301) 496-5133.

#

News Releases and Announcements Issued

MENINGITIS--The effectiveness of a vaccine to prevent bacterial meningitis caused by group A meningococci will be tested in young children in Finland under a $140,000 contract recently awarded by the National Institute of Allergy and Infectious Diseases. The meningococcus is a major cause of meningitis in young children and infection sometimes leads to neurological damage or death. Since January 1973, Finland has been experiencing a major epidemic of meningococcal group A meningitis, complicated by the fact that the bacteria involved are resistant to sulfonamides, the antibiotic preferred for treatment of this infection. Meningococcal group A meningitis has not been very common in the United States in the past few decades, although sporadic cases of this potentially epidemic disease do occur each year in this country and Canada.

FELLOWSHIPS--The Swiss National Science Foundation will make available in 1975 three year-long research fellowships to biomedical scientists who are citizens of the U.S. The fellowships will provide research experience and training in Switzerland at the postdoctoral level in basic or clinical sciences related to health. Candidates must have a doctoral degree and must have been engaged in independent responsible research. The deadline for receipt of applications is January 31, 1975 and final selection will be made at the May 1975 meeting of the Swiss National Science Foundation. Further information may be obtained from Dr. Eugene L. Walter, Jr., Swiss Research Fellowship Program, Fogarty International Center, Bldg. 31, Room 2B-59, NIH, Bethesda, Maryland 20014, Phone (301) 496-1443.

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Research Advances

IMMUNOLOGIC EVENTS IN TOOTH LOSS CHARACTERIZE OTHER INFLAMMATIONS

Tooth loss in older Americans may be related to the same series of immunologic events that characterize chronic inflammations, rheumatoid arthritis, sarcoidosis, and certain cancers affecting the lymph system.

Stephan E. Mergenhagen, Ph.D., of the National Institute of Dental Research (NIDR), recently reported this finding, which was drawn from a series of cell studies conducted by scientists at NIDR, the Walter Reed Army Institute of Dental Research, and the University of Rochester School of Medicine and Dentistry.

Teeth fall out gradually when they are surrounded by a bacteria-produced plaque which makes the supporting bone and collagen fibers vulnerable to breakdown by the enzyme collagenase. Dr. Mergenhagen, Larry M. Wahl, Sharon M. Wahl, and George R. Martin, Ph.D., of NIDR found that collagenase is produced when bacterial products called endotoxins stimulate macrophages (scavenger cells). The investigators used macrophages from guinea pigs exposed to bacterial endotoxins for their studies. They found that control macrophage cultures, without the endotoxin, did not produce collagenase.

In related studies, scientists at Walter Reed and NIDR found that destructive bone damage was increased in the presence of white blood cells of the lymphocyte type. Macrophages and lymphocytes, acting together, had an enhanced effect in producing a unique biological material called osteoclast-activating factor (OAF). (Osteoclasts are cells that destroy bone.) The finding that OAF is secreted by lymphocytes and can initiate bone loss near areas of chronic inflammation was first reported in 1972 by John

(more)

Horton, D.M.D., of Walter Reed; Lawrence G. Raisz, M.D., and Hollis A. Simmons of the University of Rochester; and Dr. Mergenhagen and Joost J. Oppenheim, M.D., of NIDR.

The investigators employed normal human white blood cells growing in tissue culture and added bone obtained from rat embryos to the fluids produced by chemically-stimulated cells. Then, they measured bone destruction by the amount of radioactively-labeled calcium released into the culture dish.

As a result, the scientists found that secretion of OAF was demonstrated in laboratory cultures of normal human lymphocytes when macrophages were added; macrophages alone failed to produce any significant amount of OAF.

Dr. Mergenhagen suggests that the newly-reported series of immunologic events in gum disease may serve as a useful model for studying other chronic inflammatory conditions. He believes that all seem to share a similar pattern of immunologic recognition and immunologic attack. Recognition of the foreign or antigenic substance is achieved by macrophages and immunocompetent nonsensitized lymphocytes: they multiply, attack, and sometimes engulf the invaders. Subsequently, various chemical defenses, such as antibodies, complement, and lymphocyte secretions such as OAF, are generated.

Previous studies by investigators from the University of Rochester, NIDR, and the National Cancer Institute point to similar immunologic activity in patients with multiple myeloma, Burkitt's lymphoma, and other cancers of the lymph system. Lymphocytes from such patients were reported to secrete a substance similar to OAF. This secretion appears distinct from hormones and

(more)

other body chemicals associated with the bone destruction that sometimes occurs with cancer.

According to Dr. Mergenhagen, elevated collagenase levels have been found in specimens from patients with rheumatoid arthritis and in sarcoidosis, as well as in patients with chronic inflammatory gum disease. He believes this adds further weight to the concept that these diseases share a common immunologic pattern.

Dr. Mergenhagen presented a report summarizing this research at the meeting of the New York Academy of Sciences, November 20, 1974.

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NOTE: For background information on this research area, see "Dental Scientists Study Mechanism of Bone Loss," NFFN, *September 10, 1974.*

Research Advances

INVESTIGATORS STUDY
HERPES SIMPLEX VIRUS

Investigators at the National Institute of Dental Research (NIDR) have shown that herpes simplex virus (HSV) can be isolated from the sensory ganglia of the nervous system of mice weeks after infection of the cornea, skin, lips, or vagina, and that injury to the nerve can reactivate the virus. Their experiments in mice provide a model for studying the different kinds of herpetic infections in humans such as fever blisters (Type 1 HSV) and genital lesions (Type 2 HSV).

Because fever blisters and other herpetic infections recur, it has long been suspected that after an initial acute infection the virus persists in sensory ganglia in a latent form. In the last two years, workers in several laboratories have isolated the virus from sensory ganglia removed from asymptomatic humans at autopsy, as well as from chronically infected animals.

Now, NIH scientists have found that sciatic nerve sectioning reactivates latent Type 1 HSV in mice. To do this, the team first infected animals by rubbing the virus into the footpad, and then attempted to recover the virus by removing spinal sensory ganglia and culturing them with virus-sensitive kidney cells. Two different methods were used for isolating the virus: a homogenization technique which kills the ganglion cells before testing for virus, and an explantation method which keeps the ganglion cells alive for three weeks.

As a result, the investigators found that virus could be recovered both by homogenizing and explanting the ganglia within the first two weeks after infection. However, in chronically infected mice (four or more weeks after

(more)

infections) the virus was only found in the living explanted neural cells and never in homogenized ganglia.

The investigators then tried to reactivate the infection by sectioning the sciatic nerve because cutting a nerve sometimes provokes herpetic lesions in patients. They theorized that since virus could not be recovered from homogenized ganglia of the chronically infected animals, the recovery of infectious virus in the homogenate following neurectomy would mean that the virus had been reactivated. Using these methods, they found that virus was reactivated in 20 of 66 animals, but was not isolated from an equal number of control animals. A sham operation near the spinal column reactivated the virus in four of 20 animals, probably as a result of unavoidable injury to the nerve. The investigators are now attempting to determine whether less severe trauma to the nerve and other types of stimuli can also reactivate the latent virus.

In addition, the team has shown that Type 2 HSV can be recovered from the sensory ganglia of female mice previously infected in the vagina and cervix. These studies with mice could serve as a model for investigation of human genital infection. More extensive research should help to answer one of the questions posed by their findings: Does the presence of a tumor in the cervix activate the latent HSV in the sensory ganglion so that the virus travels down the sensory nerves and secondarily infect the cells of that tumor?

M. Antoinette Walz, Ph.D., and Abner L. Notkins, M.D., of NIDR, and Richard W. Price, M.D., report their findings in the June 14, 1974 issue of

(more)

Science. Dr. Price, a guest worker at NIDR, is a former clinical associate of the National Institute of Neurological Diseases and Stroke.

#

GALLSTONES--Mayo Clinic scientists are testing a new method of dissolving gallstones which may someday eliminate the need for certain gallbladder surgery. The researchers, whose work is supported by the National Institutes of Health, found that chenic acid therapy produced significant reductions in gallstone size in more than half of the patients in one study.

DIVING HELMET--Scientists at the University of California, San Francisco, developed a tiny diving helmet that could save most infants born with hyaline membrane disease. The device, which supplies oxygen through continuous positive airway pressure, was the result of work supported by the National Institutes of Health.

Research Advances

INTERFERON PLAYS MAJOR ROLE IN DEFENSE AGAINST HERPES SIMPLEX

In another study of herpes simplex virus, Dr. Notkins and Donald L. Lodmell, Ph.D., of the Rocky Mountain Laboratory, National Institute of Allergy and Infectious Diseases, have found that cellular immunity, specifically the release of interferon, is required to stop the cell-to-cell spread of HSV. Previous studies of HSV have suggested that cellular immunity is involved, since HSV is known to persist in the presence of high concentrations of neutralizing antibody and most severe HSV infections are usually found in patients with deficiencies in cellular immunity. However, the precise way in which cell-mediated immunity protects against HSV has not been clear.

In former studies, Drs. Lodmell and Notkins and their associates reported that high concentrations of leukocytes added to a cell culture infected with HSV inhibited spread of the virus. The investigators designed their latest experiments to determine whether sensitized leukocytes stimulated by a specific antigen were more effective than unsensitized leukocytes in inhibiting HSV replication, and whether soluble mediators released by sensitized leukocytes could inhibit viral replication by acting on as yet uninfected cells.

The scientists found that even a few sensitized and immunologically-stimulated leukocytes added to cultures of cells infected with HSV were able to inhibit more than 90 percent of viral replication. Also, the immunologically-stimulated, sensitized cells released into the culture fluid a

(more)

substance which, by itself, could inhibit viral replication. This substance was found to have all the characteristics of the soluble mediator, interferon, which is produced naturally in the body in response to invasion by viruses or certain other intracellular parasites.

The investigators believe that results of their study support and expand the concept that the host's immunological defense against HSV consists of two phases. In the first phase, antiviral antibody, complement, and immune leukocytes react with virus or virus-infected cells. In the second phase, nonspecific cytotoxicity produced by inflammatory cells and the action of immunologically induced interferon finally stop spread of HSV. Because the virus spreads so rapidly from cell to adjacent cell, the first phase has little effect on halting the infection. Instead, it is the nonspecific second phase that stops HSV spread mainly by generating interferon.

Drs. Lodmell and Notkins published a report of their studies in the *Journal of Experimental Medicine*, September 1974.

#

INEXPENSIVE SCREENING--A scientist at the State University of New York, Buffalo, has introduced use of a filter-paper test to check newborns for sickle cell anemia. The cost of performing this blood test is only three cents. This is one of the improved screening techniques developed in work supported by the National Institutes of Health.

Photo Feature

RESEARCH PHYSICIANS SAVE INFANT LIVES

Robert Mellins, M.D., of Columbia University, and Louis Gluck, M.D., of the University of California in San Diego, are searching for ways to save infant lives.

Dr. Mellins and his associates at Columbia Presbyterian Babies Hospital in New York are studying sudden infant death syndrome (SIDS) to assess the effect of maturation and sleep on the control of respiration in normal full-term and prematurely born infants.

Since the sudden infant death syndrome is now believed to result from some abnormality in the automatic control of respiration, studies of the normal regulatory mechanisms during the first month of life will provide a basis for recognizing those infants with abnormal mechanisms who may be more prone to develop this syndrome. Recognition of the infant at higher risk is a first step in developing effective methods for prevention of this tragic condition.

Dr. Robert Mellins uses non-invasive methods that involve no patient risk to measure the ventilation and the response of ventilation to inhaled carbon dioxide in infants while awake and during various stages of natural sleep. (NIH Photo #1328)

(more)

Infants (Cont'd)

Dr. Gluck conducts research on the biochemical development of the surface-active materials (surfactant) in the developing lungs of both animals and man. He has developed a test of the amniotic fluid to assess the functional maturity of fetal lungs prior to the delivery of an infant. This test has assisted obstetricians and pediatricians in predicting the occurrence of the respiratory distress syndrome in newborn infants. The respiratory distress syndrome is the prime cause of infant mortality in the newborn period.

In his studies of amniotic fluid, Dr. Gluck hopes to determine why some abnormal pregnancy states seem to stimulate lung maturity while others appear to retard pulmonary development. His basic research on the biochemical development of the human respiratory system enables the practicing physician to better understand the state of the fetus prior to birth so that problem pregnancies may receive the needed attention to insure the best perinatal care for the newborn infant.

The SIDS studies by Dr. Mellins and Dr. Gluck's respiratory distress syndrome studies are supported by the National Institute of Child Health and Human Development.

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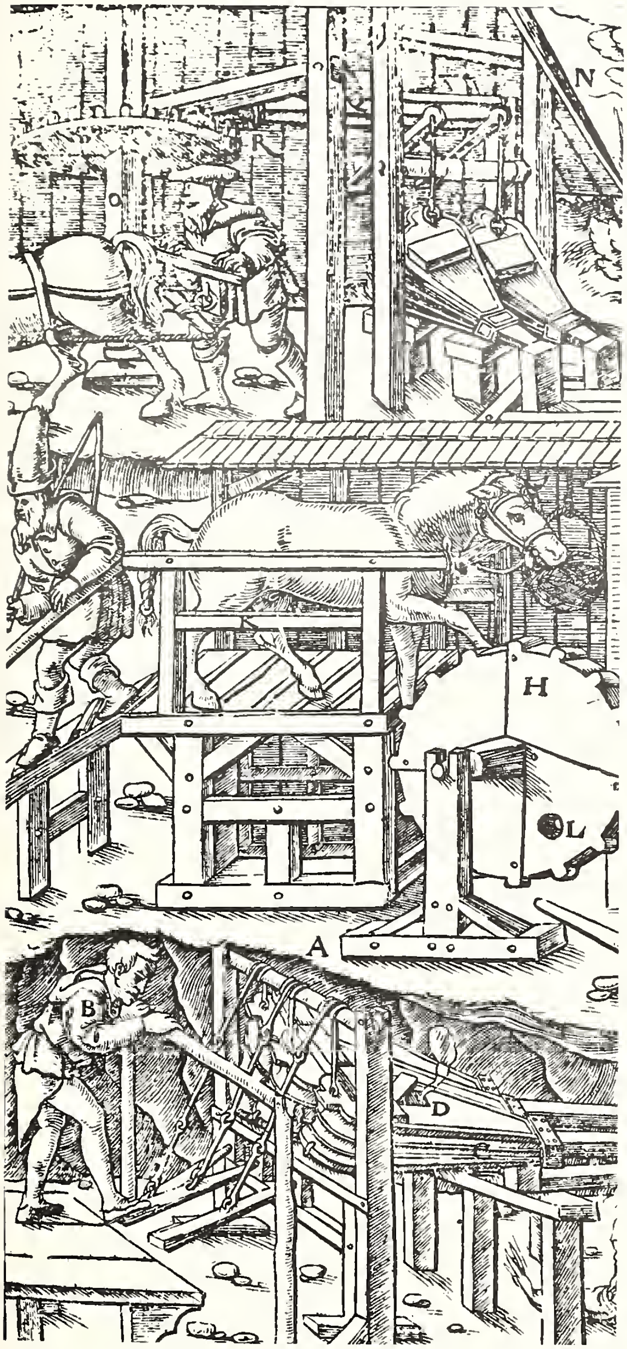
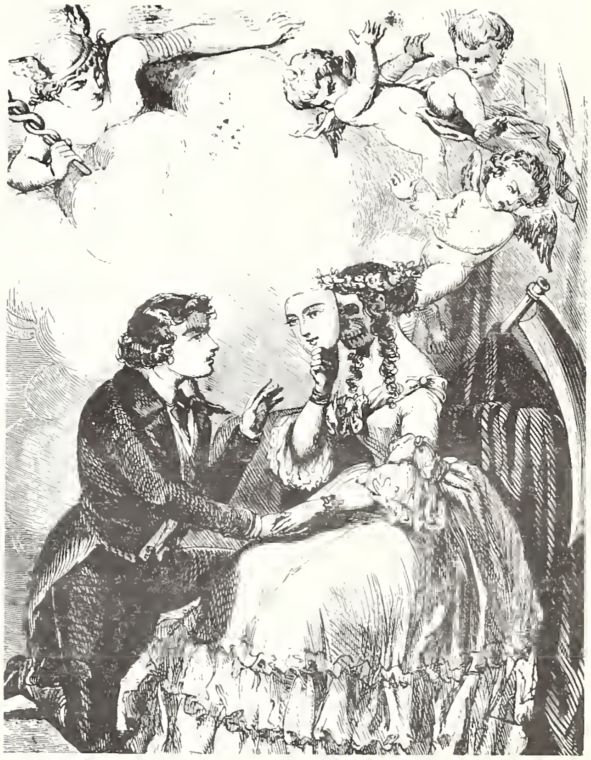
Photo Feature

In NLM Collection...

SOME HEALTH ILLUSTRATIONS DEPICT TIMELESS SUBJECTS





Many of the 55,000 illustrations in the National Library of Medicine's extensive Prints and Photographs Collection depict health subjects that are as important today as they were 100 or more years ago. This 400-year-old woodcut (left) by Agricola suggests a method of bringing fresh air to miners' lungs. Horses power the apparatus that activates the bellows. In the wood engraving (above) done by A.M. Barthelemy in 1851, the danger of venereal disease is the message. A suitor is kneeling before the figure of Death disguised as a lovely girl. The collection is open to the public. Frequent visitors are health educators, graduate students, medical writers, and book illustrators. (NIH Photos #1329, 1330)

#

News Feature

LOW MORTALITY RATE SEEN IN SKIN CANCER

Skin cancer carries the lowest mortality rate for any type of cancer even though about 300,000 new cases are reported in the United States annually.

Early detection followed by prompt, proper treatment enable about 95 percent of skin cancer patients to become free of the disease.

However, skin cancer claims 5,000 American lives each year.

There are two main kinds of skin cancer: squamous cell cancer and basal cell cancer. Basal cell cancer occurs more frequently and grows more slowly. It rarely leaves the skin, but if left untreated it can extend to the underlying bone.

Squamous cell cancer occurs much less frequently, but is a greater hazard because of its more frequent tendency to spread to other tissues and organs. From outward appearance it is often not possible to distinguish between the two types of skin cancer; in some cases they even resemble benign growths.

The exposed parts of the body--face, neck, forearms, and backs of the hands are the most common sites for skin cancer. In general, skin cancer is characterized by a pale, waxy, pearly nodule which may eventually become inflamed, ulcerate, and crust in the center. Occasionally, very early skin cancers may appear as flat, red, and sharply outlined patches.

Two main forms of skin cancer treatment are X-ray and surgery. Other treatment includes tissue destruction by electro-cautery, by freezing with liquid nitrogen, or by application of caustic chemicals.

(more)

In recent years the drug 5-fluorouracil applied to the skin as a cream or lotion has also been found useful in the treatment of superficial skin cancers. In some cases one course of treatment is sufficient; in others, repeated courses are necessary. For some patients a combination of therapies may be employed.

The sun is the leading cause of skin cancer. Other less common causes are coal tar, pitch, arsenic compounds sometimes found in well water, paraffin oil, radium, and X-rays--none of which now constitutes a major skin cancer hazard because their potential danger is understood and their use carefully regulated.

Anyone can develop skin cancer, but its most frequent victims are people with fair, ruddy, or sandy complexions who are exposed to considerable sunshine. These people should avoid excessive exposure to the sun's rays. Deliberate "tanning" not only increases the chances of skin cancer development, but also contributes to the aging appearance of the skin.

Most medical scientists agree that other factors (such as genetic factors) must be present in addition to the external forces which make certain people develop skin cancer. The National Cancer Institute is working to determine these factors, as well as seeking better methods for preventing, diagnosing, and treating squamous cell and basal cell cancer.

#

Medical News Tip

BLOOD SHUNT--University of Minnesota scientists have developed an improved arteriovenous (A-V) blood access device, or shunt, that allows blood flow in artificial kidney therapy to proceed three times faster than in standard equipment.

The new device is especially useful for patients who have been unable to maintain function in permanently implanted standard shunts. The faster flow prevents blood clotting and decreases incidence of infection. This development is part of research supported by the National Institute of Arthritis, Metabolism, and Digestive Diseases (NIAMDD).

For additional details, contact:

NIAMDD
Bldg. 31, Room 9A-04
Bethesda, MD 20014
Phone: (301) 496-3583

#

New Publication:
Drug Allergy

As more medications become available to the physician for treating illnesses, the number of adverse drug reactions increases. These reactions may be allergic in nature or may result from intolerance to the normal dose of the drug or to overdosage.

Three common drugs are the most frequent causes of drug allergy --penicillin, sulfonamides, and aspirin. These medications may be responsible for as much as 80 to 90 percent of all allergic drug reactions. Estimates of the incidence of penicillin allergy range from one to ten percent of people receiving this medication; in 1972, over 300,000 pounds of penicillin were used in the United States.

The National Institute of Allergy and Infectious Diseases has released a new publication, *Drug Allergy*, dealing with the research on this problem of modern medicine.

Science writers can obtain a copy of this publication from:

NIAID
National Institutes of Health
Bldg. 31, Room 7A-32
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December 10, 1974

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There will be no December 25 issue of NEWS & FEATURES From NIH. Publication will resume on our usual twice-monthly schedule with the issue dated January 10. Best wishes for the holiday season and the coming New Year.

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Research Advances

CATARACT STUDIES MAY LEAD TO NON-SURGICAL TREATMENT

Cataract extraction is one of the most successful surgical procedures performed today. But primarily because of social, psychological, and economic factors, cataract--a cloudiness or opacity in the normally clear lens of the eye--remains a leading cause of blindness in this country.

For this reason, NIH-supported cataract research is directed primarily at finding a non-surgical treatment and a means of preventing this disorder. Working toward this goal, Jin H. Kinoshita, Ph.D., chief of the National Eye Institute's (NEI) Laboratory of Vision Research, and associates have found that osmotic swelling is a common feature of many cataracts. In the normal lens, the state of hydration which maintains proper lens volume is controlled by two opposing forces: the permeability of the membrane which encloses the lens and a so-called pump mechanism that continually forces out sodium ions and concentrates potassium ions. According to Dr. Kinoshita, these two factors are involved in osmosis in the lens.

The fluids within the eye that bathe the lens contain a high level of sodium and a low level of potassium. However, inside the lens, high levels of potassium and low levels of sodium exist. If the osmotic process were to break down and the lens membrane were to allow a state of equilibrium to develop between these two elements, sodium would enter and potassium would leave the lens, leading eventually to swelling of the tissue. Therefore, maintaining the proper balance between extruding sodium and concentrating potassium is crucial to preserving the viability of the lens.

(more)

Dr. Kinoshita and associates investigated the sugar cataract, types of which may occur in diabetes and galactosemia, and demonstrated that lens swelling is a constant feature of the cataractous process in experimental animals. The osmotic change has been shown to be due to sugar alcohols.

In the lens, sugar is converted to sugar alcohol by the enzyme aldose reductase. Because the sugar alcohol is not further metabolized effectively, and, therefore, is not able to penetrate readily the lens membrane, it accumulates to high levels once formed in the lens fibers. The hypertonicity this creates is immediately corrected by an influx of water. The accumulation of sugar alcohol and lens swelling sets into motion the cataractous process in diabetes and galactosemia.

Dr. Kinoshita hypothesizes that because aldose reductase appears to trigger the cataractous process, it might be possible to control its formation by inhibiting the enzyme. Through research, investigators have identified a chemical that inhibits aldose reductase, and Dr. Kinoshita has successfully prevented the formation of this type of cataract in animal lenses *in vitro* and delayed its formation in the eyes of living animals.

This development led him to investigate hereditary cataracts, particularly in a special strain of mice that normally develops a small lens opacity three weeks after birth. Dr. Kinoshita observed that at the same time this opacity develops, a sudden increase in lens hydration as well as a rise in the sodium level occurs. He and his associates found that the failure to exclude sodium becomes more prominent as the cataract progresses.

(more)

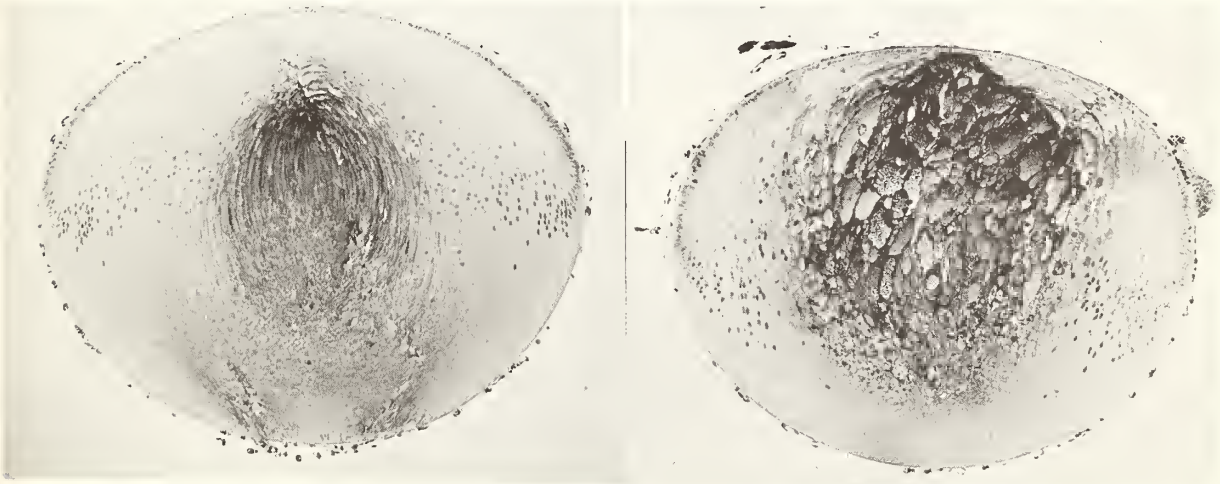
Cataract (Cont'd)

In further work, the researchers showed that the activity of the enzyme Na-K ATPase (sodium-potassium adenosine triphosphate) is reduced in the lenses of these cataractous mice. (Na-K ATPase is the key enzyme involved in maintaining lens hydration.) The investigators also found that this enzyme is normal in the animal's other body tissues. This led Dr. Kinoshita to hypothesize that a cataract-inducing factor is present in the lenses of these mice. His studies revealed that a substance is present in the cataract which inactivates ATPase.

If Dr. Kinoshita's theory proves correct, it may be possible to find a means of preventing the inactivation of the enzyme and, thus, open the possibility of delaying the formation of or even preventing this form of cataract.

Spurred by these findings, Dr. Kinoshita is also investigating the cause of the most common form of cataract, senile cataract. He and other

(more)



A normal mouse lens (18-day embryo) shown in the left photo, is contrasted to a Fraser mouse cataract (18-day embryo) in the right photo. (NIH Photos #1331, 1332)

Cataract (Cont'd)

NEI-supported investigators are concentrating efforts on determining what causes the lens to become opaque in this cataract associated with aging. Through this research, it may someday be possible by medical means to prevent or slow the development of this common cause of visual disability and blindness.

Dr. Kinoshita's findings, presented as the Proctor Award Lecture to the Association for Research in Vision and Ophthalmology, appear in *Investigative Ophthalmology*, October 1974.

#

EYE SURGERY--A tiny motor-driven instrument, the VISC, is helpful in treating patients blinded by vitreal diseases and certain retinal diseases affecting the vitreous. The device was developed by University of Miami scientists whose work is funded by the National Institutes of Health.

DIGESTIVE DISORDER--Diverticulosis is a condition of the digestive tract characterized by tiny mucous membrane sacs (diverticula) that protrude through the muscular wall of the large intestine. If these sacs become infected, the condition is known as diverticulitis, according to the National Institutes of Health.

Photo Feature

ULTRAFILTRATION CELL OFFERS NEW FORM OF FLUID REMOVAL

An ultrafiltration cell has been designed to remove excess sodium and water efficiently, rapidly, and inexpensively from fluid-overloaded patients on chronic hemodialysis.

Scientists at the University of Pennsylvania, supported by a contract from the Artificial Kidney Program of NIH's National Institute of Arthritis, Metabolism, and Digestive Diseases, recently developed such a device which can be used as a separate unit or in series with an artificial kidney. The cell may also enable physicians to treat more rapidly and efficiently those patients whose edema is secondary to cardiac failure and those with acute pulmonary edema that previously required emergency hemodialysis or prolonged treatment with diuretics and sodium and fluid restriction.

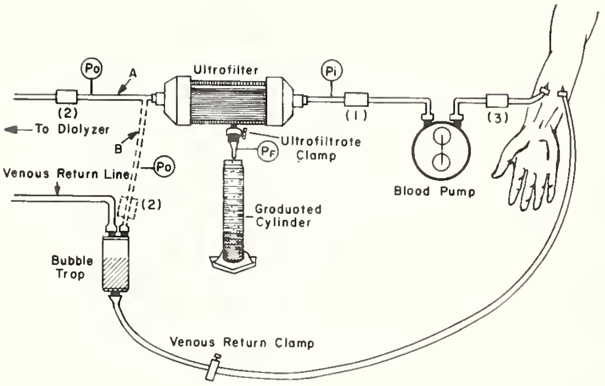
In an evaluation of the device, the researchers found that the ultrafiltration cell provides a safer and better controlled form of fluid removal than either peritoneal dialysis or hemodialysis. With the device, the exact volume of fluid removed can be identified in a graduated cylinder, and the flow rate can be controlled and varied on a minute-to-minute basis. This short-term procedure also minimizes protein loss and results in no change in plasma electrolytes or acid-base balance.

Treatment for patients with chronic congestive heart failure has in the past consisted of administering diuretic agents or low salt diets which required a stay of days or weeks in a hospital. With use of the ultrafiltration cell, however, the costly hospitalization could be replaced with one or two ultrafiltration treatments of six to eight hours. The portable, sterile,

(more)

prepackaged unit could also be available for use in the emergency room and intensive care units as well as in a hemodialysis unit.

The investigators note that complications with the ultrafiltration cell are rare although leg cramps and post ultrafiltration orthostatic hypotension have occurred with ultrafiltration rates of greater than 300 ml per hour. How rapidly the fluid is removed depends on the patient's individual response to the treatment as well as the medical urgency. Careful monitoring is required to avoid possible hazards that may accompany this or any other fluid removal procedure.



This schematic diagram illustrates the ultrafiltration system. The cell can be used in series with the artificial kidney (A) or as a separate unit (B). (NIH Photo #1333)

The investigators--Marc Eliot Silverstein, M.D., Cheryl A. Ford, Michael J. Lysaght, and Lee W. Henderson, M.D.--published a report of their analysis of the ultrafiltration cell in *The New England Journal of Medicine*, October 10, 1974.

#

This article was prepared by Dorothy Mastin, *a University of Maryland student, while on a journalism internship in the News Branch, NIH.*

Research Advances

STUDY NEGATES LINK BETWEEN COFFEE AND HEART DISEASE

Investigators associated with the Framingham Heart Study recently reported that coffee drinking is not a factor in the development of atherosclerotic cardiovascular disease. Their research indicates that six cups of coffee a day and possibly even more do not increase the risk of developing common forms of circulatory disease or heart attacks that may result in sudden death.

Coffee-drinking habits were determined at the fourth biennial examination (1955-1958) of the Framingham Study. The subjects, 1,992 males and 2,500 females 35 to 69 years of age, were free of any circulatory and heart disorders at the time of the exam. The scientists measured the incidence of coronary heart disease and other cardiovascular diseases over a 12-year period.

The scientists studied coffee drinking in relation to total coronary heart disease, angina pectoris, myocardial infarction, sudden death, and death from all causes. Only for male subjects and only in the category "death from all causes" did the investigators observe a significant increase in the risk with increasing coffee consumption. The research showed an increase in the risk of death from slightly below that expected in male non-coffee drinkers to above that expected in those males drinking four or more cups per day. But the investigators noted that it was not clear whether the increase was attributed to the coffee intake or to some other associated factor. Their study showed the only variable in this group closely

(more)

Coffee (Cont'd)

related to coffee drinking was cigarette smoking. The non-coffee drinkers smoked 8.7 cigarettes per day as compared to those drinking more than seven cups and smoking 21.8 cigarettes per day. After further examination, the scientists concluded that the relation of overall mortality to the level of coffee consumption is based on the association between coffee drinking and cigarette smoking.

They found added support for their findings when no trend relating death from all causes and coffee consumption was observed in women--a group that also reflects a generally lower cigarette consumption.

The research showed no significant relation between coffee intake and the relative risk of development of coronary heart disease in men and women. The data also produced a negative relation between coffee consumption and the development of stroke.

The scientists indicate, however, that their study does not consider the possible effect of coffee intake on the course of existing cardiovascular disease. They note the need for further research regarding this aspect of the problem.

The investigators--Thomas R. Dawber, M.D., M.P.H., William B. Kannel, M.D., M.P.H., and Tavia Gordon--worked with participants in the Framingham Heart Study, begun in 1949 by the National Heart and Lung Institute.

The report of their observations of coffee-drinking and cardiovascular disease is published in *The New England Journal of Medicine,* October 24, 1974.

#

Photo Feature

SUMEX FACILITY TO COMPUTERIZE ARTIFICIAL INTELLIGENCE IN MEDICINE

SUMEX, the Stanford University Medical Experimental Computer, was recently dedicated. This Division of Research Resources (DRR) facility is the first nationally shared computer facility to focus on the use of artificial intelligence in medicine. Stanford's artificial intelligence research is directed toward computerizing information processing tasks generally considered to require human intelligence, such as the cognitive activities associated with glaucoma control and the recognition of paranoid behavior. Above, Nobel Laureate Joshua Lederberg, Ph.D., principal investigator of SUMEX, works at the SUMEX terminal. The facility is supported by a $2.5 million, five-year grant from DRR. (NIH Photo #1334)

#

Photo Feature

NEW BLOOD TEST DETECTS REJECTION IN HEART TRANSPLANT PATIENTS

A new blood test that acts as "an early warning system" for detecting graft rejection in heart transplant patients has been developed by surgeons at Stanford University School of Medicine.

Five patients were studied with the new test, the modified reactive leukocyte blastogenesis (MRLB) assay. The patients were monitored for 45 to 75 days after they had received heart transplants at Stanford University Hospital. There were 18 documented rejection episodes in these patients.

The MRLB test predicted rejection almost five days earlier than either electrocardiogram or heart tissue biopsies, the two other methods now being used to detect rejection. The new test continued to be as sensitive in predicting subsequent episodes, the researchers reported.

The surgeons believe that detecting rejection in its earliest stages would require less medication to reverse it. This would lessen risk to the patient. Drugs now used to suppress the immune reaction reverse rejection, but they also predispose patients to infections and malignancies.

Tissue rejection in the body is a two-stage process. First, immune cells begin to multiply. Later, the immune cells invade the graft and destroy it. The MRLB test detects immune cell division as soon as it gets under way by monitoring the synthesis of DNA (deoxyribonucleic acid), the hereditary material of cells that is essential for division.

(more)

Blood Test (Cont'd)

Eugene Dong, Jr., M.D., associate professor of cardiovascular surgery at Stanford University School of Medicine, reviews data on a new blood test for heart transplant rejection with Randall E. Morris, a fourth-year medical student. Morris reported the development of this new test at the recent meeting of the American College of Surgeons in Miami. (NIH Photo #1335)

To monitor DNA synthesis, a blood sample is obtained as often as needed from the patient and incubated in a test tube containing nutrients essential for the growth of blood cells outside the body. The incubation solution contains a radioactively labeled DNA building block (tritiated thymidine). Actively dividing cells incorporate the thymidine into their newly synthesized DNA, indicating that the immune system is being mobilized and antirejection treatment should begin.

This research, under the direction of Eugene Dong, Jr., M.D., is funded by the National Heart and Lung Institute.

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Photo Feature

Kidney Tumors...

NEW DIAGNOSTIC TECHNIQUE MAY ELIMINATE SURGERY

Unnecessary surgery for more than 100,000 patients with suspected kidney tumors may be avoided due to a new diagnostic technique.

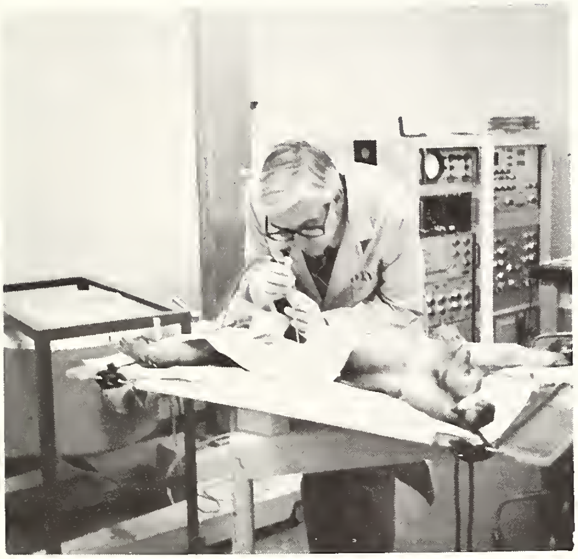
The technique, developed by James A. Roberts, M.D., head of the Urology Department of the Delta Regional Primate Research Center, Covington, Louisiana, involves use of various types of endoscopes which have been used for visual examination of suspected diseased kidneys in monkeys. The Delta Center is supported by the NIH Division of Research Resources.

According to Dr. Roberts, his research with monkeys convinced him that the endoscope could be used to examine human patients with suspected cysts of the kidney. Because of the established association of cysts with malignant tumors in about two percent of such cases, it is necessary to make an accurate diagnosis. By using the endoscope, the scientist can now rule out the presence of malignant tumors in most cases without resorting to surgery.

Dr. Roberts' endoscope technique, utilizing a 2.2 millimeter needlescope, provides a quick and easy diagnosis. The renal cyst is punctured below the 12th rib with the instrument (instead of the usual one millimeter needle used for renal cyst puncture), and the interior of the cyst may be visualized to rule out tumor. Dr. Roberts hopes that this addition to endoscope equipment and techniques for human patients will increase diagnostic accuracy past the present 98 percent in cases of suspected kidney tumor.

(more)

Diagnostic Technique (Cont'd)



In the photo above, Dr. Roberts examines a large rhesus monkey at the Delta Regional Primate Research Center using a needlescope. It was this work with nonhuman primates that led him to realize that the same technique could be used effectively to examine human patients with suspected cancer of the kidneys. (NIH Photo #1336) At right, Dr. Roberts demonstrates the new technique for performing a renal cystoscopy on a human patient. Dr. Roberts did his clinical work in hospitals associated with the Tulane University Medical Center. (NIH Photo #1337)

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Medical News Tip

HISTOCOMPATIBILITY ANTIGENS--The National Heart and Lung Institute (NHLI) is supporting efforts to prevent the sensitization of the transplant patient by lowering or eliminating histocompatibility antigens (HL-A) in transfused blood.

Current studies of *in vitro* methods for removing HL-A will be followed by clinical trials on renal dialysis patients to determine if sensitization to HL-A can be reduced or prevented.

One of the methods of removing HL-A from blood is freezing blood. This method appears to destroy HL-A with maximum preservation of red cells, but the usefulness of this method is limited by cost factors and the availability of freezing facilities. Another method that is now being evaluated involves a double centrifugation process.

For additional details, contact:

NHLI
Bldg. 31, Room 5A21
Bethesda, MD 20014
Phone: (301) 496-4236

#

News Releases Issued

CANCERLINE--The National Cancer Institute (NCI) and the National Library of Medicine have jointly developed a computerized information service to provide scientists with easy access to information on cancer treatment research. Called CANCERLINE, the computer system contains approximately 16,000 abstracts from the NCI publication *Cancer Chemotherapy Abstracts*. These abstracts summarize research reports published between 1967 and 1972 on the treatment of human and animal cancers. By early 1975, the CANCERLINE system will contain about 5,000 additional therapy abstracts for 1973 and 1974, approximately 18,000 *Carcinogenesis Abstracts*, and 6,000 descriptions of ongoing cancer research projects. For information on how to use the CANCERLINE system, contact: International Cancer Research Data Bank Program Office, NCI, Bldg. 31, Room 10A35, Bethesda, MD 20014, phone (301) 496-2713.

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